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(54) Title: PHARMACEUTICAL COMPOUNDS

(57) Abstract: The present invention relates to the use of certain 4-substituted pyrimidine derivatives as mGluR1 antagonists, to novel 4-substituted pyrimidine derivatives, to pharmaceutical formulations comprising 4-substituted pyrimidine derivatives, to a process for preparing 4-substituted pyrimidine derivatives and to intermediates useful in the preparation of 4-substituted pyrimidine derivatives.

PHARMACEUTICAL COMPOUNDS

The present invention relates to pharmaceutical compounds. More particularly it relates to the use of certain 4-substituted pyrimidine derivatives as mGluR1 antagonists, to novel 4-substituted pyrimidine derivatives, to pharmaceutical formulations comprising 4-substituted pyrimidine derivatives, to a process for preparing 4-substituted pyrimidine derivatives and to intermediates useful in the preparation of 4-substituted pyrimidine derivatives.

In the mammalian central nervous system (CNS), the transmission of nerve impulses is controlled by the interaction between a neurotransmitter, that is released by a sending neuron, and a surface receptor on a receiving neuron, which causes excitation of this receiving neuron. L-Glutamate, which is the most abundant neurotransmitter in the CNS, mediates the major excitatory pathway in mammals, and is referred to as an excitatory amino acid (EAA). The receptors that respond to glutamate are called excitatory amino acid receptors (EAA receptors). See Watkins & Evans, *Ann. Rev. Pharmacol. Toxicol.*, 21, 165 (1981); Monaghan, Bridges, and Cotman, *Ann. Rev. Pharmacol. Toxicol.*, 29, 365 (1989); Watkins, Krogsgaard-Larsen, and Honore, *Trans. Pharm. Sci.*, 11, 25 (1990). The excitatory amino acids are

of great physiological importance, playing a role in a variety of physiological processes, such as long-term potentiation (learning and memory), the development of synaptic plasticity, motor control, respiration, cardiovascular regulation, and sensory perception.

Excitatory amino acid receptors are classified into two general types. Receptors that are directly coupled to the opening of cation channels in the cell membrane of the neurons are termed "ionotropic". This type of receptor has been subdivided into at least three subtypes, which are defined by the depolarizing actions of the selective agonists *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainic acid (KA). The second general type of receptor is the G-protein or second messenger-linked "metabotropic" excitatory amino acid receptor. This second type is coupled to multiple second messenger systems that lead to enhanced phosphoinositide hydrolysis, activation of phospholipase D or C, increases or decreases in c-AMP formation, and changes in ion channel function. Schoepp and Conn, *Trends in Pharmacol. Sci.*, 14, 13 (1993). At least eight subtypes of metabotropic glutamate receptor, identified as mGluR1, 2, 3, 4, 5, 6, 7 and 8, have been cloned and these have been classified into three groups according to the second messenger system to which they are coupled, their sequence homology and their agonist selectivity. Pin, J.P. and Duvoisin, R. (1995) Neuropharmacology, 34, 1-26. The first of these three groups, Group I, contains the mGluR1 and mGluR5 subtypes. These subtypes are coupled to phosphoinositide (PI) hydrolysis and are predominantly located on the postsynaptic terminal. The second and third of these three groups, Group II and Group III, contain respectively mGluR2 and 3 and mGluR4, 6, 7 and 8. They are negatively coupled to adenyl cyclase and are thought to act presynaptically, as autoreceptors, regulating glutamate transmission.

Both ionotropic and metabotropic types of receptors appear not only to mediate normal synaptic transmission along excitatory pathways, but also participate in the modification of synaptic connections during development and throughout life. Schoepp, Bockaert, and Sladeczek, *Trends in Pharmacol. Sci.*, 11, 508 (1990); McDonald and Johnson, *Brain Research Reviews*, 15, 41 (1990).

The excessive or inappropriate stimulation of excitatory amino acid receptors leads to neuronal cell damage or loss by way of a mechanism known as excitotoxicity. This process has been suggested to mediate neuronal degeneration in a variety of conditions. The medical consequences of such neuronal degeneration makes the abatement of these degenerative neurological processes an important therapeutic goal.

The metabotropic glutamate receptors are a highly heterogeneous family of glutamate receptors that are linked to multiple second-messenger pathways. These receptors function to modulate the presynaptic release of glutamate, and the postsynaptic sensitivity of the neuronal cell to glutamate excitation. Compounds which modulate the function of these receptors, in particular agonists and antagonists of glutamate, are useful for the treatment of acute and chronic neurodegenerative conditions, and as antiischaemic, antipsychotic, anticonvulsant, analgesic, anxiolytic, antidepressant, and anti-emetic agents.

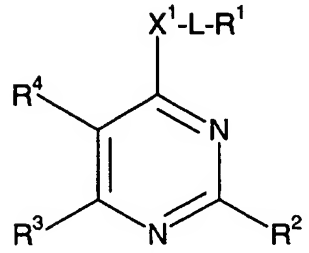
International patent application publication number WO 99/26927, published on 3rd June, 1999 discloses that compounds of formula

R-[Linker]-Ar

in which R, Ar and [Linker] are very broadly defined, are useful as Group I metabotropic glutamate receptor antagonists.

Surprisingly, certain 4-substituted pyrimidine derivatives have now been found to act as antagonists of glutamate at mGluR1 receptors.

According to one aspect, therefore, the present invention provides the use of a compound of general formula



I

in which:

X^1 represents O or NH;

L represents a bond or a (1-6C)alkylene chain optionally interrupted by O, S, SO, SO_2 or NH and optionally substituted on an alkylene carbon atom by fluoro, hydroxy, (1-4C)alkoxy or oxo;

R^1 represents an unsubstituted or substituted carbocyclic or heterocyclic group;

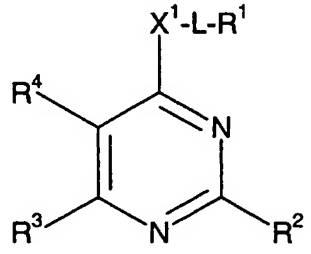
R^2 represents a hydrogen atom, a halogen atom, a carboxyl group, a cyano group or a group of formula X^2-R^5 in which X^2 represents a bond, O, S, SO, SO_2 or NH and R^5 represents (1-8C)alkyl, (3-10C)cycloalkyl, halo(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkanoyl(1-4C)alkyl, (1-4C)alkanoyloxy(1-4C)alkyl, carboxy(1-4C)alkyl, (1-4C)alkylaminocarbonyl(1-4C)alkyl, (1-4C)alkanoylamino(1-4C)alkyl, (1-4C)alkylthio(1-4C)alkyl, (1-4C)alkylsulfinyl(1-4C)alkyl, (1-4C)alkylsulfonyl(1-4C)alkyl, (1-4C)alkylsulfonylamino)(1-4C)alkyl, (1-4C)alkylamino-sulfonyl)(1-4C)alkyl, di(1-4C)alkylaminophosphonyl)(1-4C)alkyl, phenyl or phenyl(1-4C)alkyl in which any phenyl group is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, (1-4C)alkyl and (1-4C)alkoxy; and

R^3 and R^4 each independently represents (1-4C)alkyl or together with the carbon atoms to which they are attached form an unsubstituted or substituted carbocyclic or heterocyclic ring;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for the treatment of a condition indicating administration of an mGluR1 antagonist.

In addition, the present invention provides the use of a compound of general formula



I

in which

X^1 represents O or NH;

L represents a bond or a (1-6C)alkylene chain optionally interrupted by O, S, SO, SO_2 or NH and optionally substituted on an alkylene carbon atom by fluoro, hydroxy, (1-4C)alkoxy or oxo;

R^1 represents an unsubstituted or substituted carbocyclic or heterocyclic group;

R^2 represents a hydrogen atom, a halogen atom, a carboxyl group, a cyano group, a SCH_2CN, or a group of formula X^2-R^5 in which X^2 represents a bond, O, S, SO, SO_2 or NH and R^5 represents (1-8C)alkyl, (3-10C)cycloalkyl, halo(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkanoyl(1-4C)alkyl, (1-4C)alkanoyloxy(1-4C)alkyl, carboxy(1-4C)alkyl, (1-4C)alkylaminocarbonyl(1-4C)alkyl, (1-4C)alkanoylamino, (1-4C)alkanoylamino(1-4C)alkyl, (1-4C)alkanoylamino[(1-4C)alkyl]$_2$, (1-

4C)alkylthio(1-4C)alkyl, (1-4C)alkylsulfinyl(1-4C)alkyl, (1-4C)alkylsulfonyl(1-4C)alkyl, (1-4C)alkylsulfonylamino)(1-4C)alkyl, (1-4C)alkylamino-sulfonyl)(1-4C)alkyl, di(1-4C)alkylaminophosphonyl)(1-4C)alkyl, phenyl or phenyl(1-4C)alkyl in which any phenyl group is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, (1-4C)alkyl and (1-4C)alkoxy; and

R^3 and R^4 each independently represents (1-4C)alkyl or together with the carbon atoms to which they are attached form an unsubstituted or substituted carbocyclic or heterocyclic ring;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for the treatment of a condition indicating administration of an mGluR1 antagonist.

According to another aspect, the present invention provides a method of antagonizing the action of glutamate at mGluR1 receptors in a patient requiring such treatment, which comprises administering an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined herein.

As used herein, the term "effective amount" refers to the amount of a compound of formula I which is effective, upon single or multiple dose administration to a patient, in treating the patient suffering from the named disorder.

The particular effective amount or dose of compound administered according to this invention will of course be determined by the particular circumstances surrounding the case, including the compound administered, the route of administration, the particular condition being treated, and similar considerations. The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, or intranasal routes. Alternatively, the compound may be administered by

continuous infusion. A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of the active compound of this invention. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 25 mg/kg.

A variety of physiological functions have been shown to be subject to influence by excessive or inappropriate stimulation of excitatory amino acid transmission. The formula I compounds of the present invention are believed, through their action as mGluR1 antagonists, to have the ability to treat a variety of neurological disorders in mammals associated with this condition, including acute neurological disorders such as cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord lesions due to trauma or infarction/ischaemia or inflammation, head trauma, perinatal hypoxia, cardiac arrest, and hypoglycemic neuronal damage, and chronic neurological disorders, such as Alzheimer's disease, Huntington's Chorea, inherited ataxias, amyotrophic lateral sclerosis, AIDS-induced dementia, ocular damage and retinopathy, cognitive disorders, Parkinson's Disease, drug-induced Parkinsonism and essential tremor. The present invention also provides methods for treating these disorders which comprises administering to a patient in need thereof an effective amount of a compound of formula I, or a pharmaceutically acceptable salt thereof.

The formula I compounds of the present invention are also believed, through their action as mGluR1 antagonists, to have the ability to treat a variety of other neurological disorders in mammals that are associated with glutamate dysfunction, including muscular spasms, convulsions (such as epilepsy), spasticity, migraine (including menstrual migraine), urinary incontinence, psychosis, (such as schizophrenia or bipolar disorder), post traumatic stress

disorder, depression, drug tolerance and withdrawal (such as alcohol, nicotine, opiates and benzodiazepines), drug intoxication, metabolic derangement, anxiety and related disorders, emesis, brain edema, tardive dyskinesia and pain. Therefore, the present invention also provides methods for treating these disorders which comprise administering to a patient in need thereof an effective amount of the compound of formula I, or a pharmaceutically acceptable salt thereof.

The forms of pain that may be treated in accordance with the present invention include those arising as a result of central sensitization or peripheral sensitization of pain transmitting pathways. These forms of pain include post-operative pain; dental pain; menstrual pain; migraine pain; persistent headaches, such as cluster headache or chronic tension headache; persistent pain states such as fibromyalgia or myofascial pains; neuropathic pain such as painful diabetic neuropathy; trigeminal neuralgia; postherpetic neuralgia; back pain; cancer pain; arthritic pain such as pain due to osteoarthritis or rheumatoid arthritis; bursitis; pain associated with AIDS; visceral pain, such as interstitial cystitis and IBS; pain due to spinal trauma and/or degeneration; post-stroke pain; burn pain; pain associated with muscle, nerve, skin, joint or bone; conditions such as allodynia; hyperalgesia; hypersensitization to pain signals; referred pain; enhanced memory of pain and neuronal mechanisms involved in coping with pain.

The term "treating", for purposes of the present invention, includes prophylaxis of a named condition, and amelioration or elimination of a named condition once the condition has been established.

The term "patient" for purposes of the present invention is defined as any warm blooded animal such as, but

not limited to, a mouse, guinea pig, dog, horse, or human. Preferably, the patient is human.

Referring to the compounds of formula I, unless specified otherwise, the term "alkyl" as used herein means a straight chain or branched alkyl group. Examples of values for a (1-8C)alkyl group include (1-6C)alkyl and (1-4C)alkyl such as methyl, ethyl, propyl, isopropyl, butyl and isobutyl.

The term (1-6C)alkylene chain optionally interrupted by O, S, SO, SO_2 or NH and optionally substituted on an alkylene carbon atom by fluoro, hydroxy, (1-4C)alkoxy or oxo refers to a straight chain or branched divalent group in which one, two or more groups in the chain may be replaced by O, S, SO, SO_2 or NH and in which one or two chain carbon atoms may bear fluoro, hydroxy, (1-4C)alkoxy or oxo. The term (1-6C)alkylene includes a group of formula $C_mH_{2m}-(X_3)_q-C_nH_{2n}$ in which X^3 is O, S, SO, SO_2, NH, CHF, CF_2, CHOH, CH(O(1-4C)alkyl) or CO, q is 0 or 1, and each of m and n is 0 or an integer of from 1 to 4, provided that when q is 1 and X^3 is O, S, SO, SO_2 or NH, m is at least 2. Examples of particular values include ethylene, propylene, butylene, methylthioethylene, and methylsulphonylethylene.

The term halo(1-6C)alkyl refers to an alkyl group in which one or more hydrogen atoms have been replaced by a halogen atom or atoms. Examples of a halo(1-6C)alkyl group are trifluoromethyl and fluoroethyl.

The term (1-4C)alkoxy refers to an alkoxy radical made up of an oxygen radical bearing a saturated straight or branched chain hydrocarbon radical of one to four carbon atoms. Included within the scope of this term are methoxy, ethoxy, propoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy and the like.

The term halogen atom refers to a fluorine, chlorine, bromine or iodine atom.

As used herein without further qualification, the term unsubstituted or substituted, for example in the term unsubstituted or substituted carbocyclic or heterocyclic group or ring, refers to a group that is unsubstituted or substituted by one, two or more substituents, said substituents being selected from atoms and groups which, when present in the compound of formula I, do not prevent the compound of formula I from functioning as a antagonist of mGluR1 receptor subtype function.

Examples of atoms and groups which may be present in a substituted carbocyclic or heterocyclic group or ring are oxo, methylenedioxy, a halogen atom, a nitro group, a cyano group, a (1-4C)alkyl group, a halo(1-4C)alkyl group, or a group of formula -X-R in which X represents O, S, SO, SO_2, NR^z, CO, COO, OCO, CONH, NHCO, SO_2NH, or $NHSO_2$ and R represents a hydrogen atom, a (1-8C)alkyl group, a (3-10C)cycloalkyl group, a morpholino group, a phenyl group, a phenyl(1-4C)alkyl group or a phenyl(2-4C)alkenyl group in which any phenyl group is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a (1-4C)alkoxy group. Examples of particular values include chlorine, bromine, methyl, ethyl, methoxy, 2-methyl-3-prop-2-enoyl, morpholinocarbonyl, cyclohexylaminocarbonyl, adamantylaminocarbonyl, benzylaminocarbonyl, and benzyloxycarbonyl.

The term carbocyclic group includes an aromatic group, a non-aromatic group or a non-aromatic group fused with an aromatic group.

The term aromatic group includes phenyl and a polycyclic aromatic carbocyclic ring such as 1-naphthyl or 2-naphthyl.

A carbocyclic group that is a non-aromatic group may be, for example a (3-10C)cycloalkyl group or a (3-10C)cycloalkenyl group.

The term (3-10C)cycloalkyl refers to a monocyclic or polycyclic group. Examples of particular values include cyclopentyl, cyclohexyl, bicyclo[2.2.1]hept-2-yl, bicyclo[3.1.1]hept-2-yl and adamantyl.

The term (3-10C)cycloalkenyl refers to a monocyclic or polycyclic group. Examples of particular values include bicyclo[2.2.1]hept-2-ene-4-yl.

A carbocyclic group that is a non-aromatic group fused with an aromatic group may be, for example, a (3-10C)cycloalkyl group fused with a benzene ring, such as 2,3-dihydro-1H-indenyl or 1,2,3,4-tetrahydronaphthyl.

Examples of particular values for a carbocyclic group are phenyl, 1-naphthyl, 2-naphthyl, cyclopentyl, cyclohexyl, bicyclo[2.2.1]hept-2-yl, bicyclo[3.1.1]hept-2-yl, adamantyl, 2,3-dihydro-1H-inden-1-yl, 2,3-dihydro-1H-inden-2-yl, and bicyclo[2.2.1]hept-2-ene-4-yl.

The term heterocyclic group includes a non-aromatic group and a heteroaromatic group.

The term non-aromatic heterocyclic group includes a saturated or partially unsaturated 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, and a bicyclic group consisting of a saturated or partially unsaturated 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen fused with a benzene ring. An example of a non-aromatic heterocyclic group is 1,3-dihydro-2H-isoindol-2-yl.

The term heteroaromatic group includes an aromatic 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, and a bicyclic group consisting of a 5-6 membered ring containing from one

to four heteroatoms selected from oxygen, sulfur and nitrogen fused with a benzene ring or a 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen. Examples of heteroaromatic groups are furyl, thiophenyl, oxazolyl, isoxazolyl, thiazoyl, isothiazolyl, imidazolyl, pyrimidyl, benzofuryl, benzothiophenyl, benzimidazolyl, benzoxazolyl, benzothiazolyl and indolyl.

Examples of particular values for an unsubstituted or substituted carbocyclic or heterocyclic group are phenyl, 2-chlorophenyl, 2,6-dichlorophenyl, 2-methoxyphenyl, 4-methoxyphenyl, bicyclo[2.2.1]hept-2-yl, (1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-2-yl, 2,3-dihydro-1H-inden-1-yl and 2,3-dihydro-1H-inden-2-yl.

In the compounds of formula I, X^1 preferably represents NH.

L preferably represents a bond or a group of formula C_mH_{2m}-$(X_3)_q$-C_nH_{2n} in which X^3 is O, S, SO, SO_2, NH, CF_2, CHOH, CH(O(1-4C)alkyl) or CO, q is 0 or 1, and each of m and n is 0 or an integer of from 1 to 4, provided that when q is 1 and X^3 is O, S, SO, SO_2 or NH, m is at least 2. Preferably X^3 is S or SO_2, q is 0 or 1, m is 2 and n is 0, 1 or 2.

Examples of particular values for L are a bond, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)CH_2-$, $-(CH_2)_2SCH_2-$, $-(CH_2)_2)SO_2CH_2-$, $-CH(CH_2CH_3)CH_2OCH_2-$, $-CH_2CHF-$, $-CH_2CF_2-$, $-CH_2CH(OH)-$ and $-CH_2CO-$. The values of a bond, $-(CH_2)_2-$, $-(CH_2)_2SCH_2-$ are especially preferred for L, with $-(CH_2)_2-$ being most especially preferred.

R^1 preferably represents an unsubstituted or substituted carbocyclic group in which the carbocyclic group is selected from an aromatic group, a non-aromatic group and a non-aromatic group fused with an aromatic group.

The carbocyclic group is preferably selected from phenyl which is unsubstituted or substituted by one or two

substituents selected independently from a halogen atom, a (1-4C)alkyl group and a (1-4C)alkoxy group; (3-10C)cycloalkyl which is unsubstituted or substituted by from one to three methyl groups; 2,3-dihydro-1H-indenyl; and 1,2,3,4-tetrahydronaphthyl.

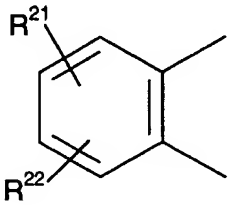
Examples of particular values for R^1 are phenyl, 2-chlorophenyl, 3-bromophenyl, 2,6-dichlorophenyl, 2-chloro-4-fluorophenyl, 2-methylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 4-phenylphenyl, cyclohexyl, bicyclo[2.2.1]hept-2-yl, (1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-2-yl, adamantyl, 2,3-dihydro-1H-inden-1-yl, 2,3-dihydro-1H-inden-2-yl and 1,2,3,4-tetrahydronaphth-1-yl.

R^2 preferably represents a hydrogen atom, a halogen atom, a carboxy group, a cyano group, or a (1-8C)alkyl, halo(1-6C)alkyl, (1-6C)alkoxy, hydroxy(1-6C)alkoxy, (1-6C)alkylthio, (1-4C)alkylsulfonyl, (1-4C)alkylamino, halo(1-4C)alkylthio, hydroxy(1-4C)alkylthio, dihydroxy(1-4C)alkylthio, (1-4C)alkoxy(1-4C)alkylthio, (1-4C)alkanoyl(1-4C)alkylthio, (1-4C)alkoxycarbonyl(1-4C)alkylthio, carboxy(1-4C)alkylthio, (1-4C)alkylaminocarbonyl(1-4C)alkylthio, (1-4C)alkanoylamino(1-4C)alkylthio, (1-4C)alkylaminosulfonyl)(1-4C)alkylthio, di(1-4C)alkylaminophosphonyl)(1-4C)alkylthio, or phenyl(1-4C)alkylthio in which the phenyl group is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, (1-4C)alkyl and (1-4C)alkoxy.

Examples of particular values for R^2 are hydrogen, chlorine, carboxy, cyano, methyl, ethyl, propyl, isopropyl, isobutyl, trifluoromethyl, ethoxy, 2-hydroxyethyl, ethylamino, 2-fluoroethylthio, methylthio, ethylthio, propylthio, isobutylthio, 2-hydroxyethylthio, 2-hydroxypropylthio, 2,3-dihydroxypropylthio, 2-

methoxyethylthio, ethanoylmethylthio, 2-methoxycarbonyl-methylthio, 2-carboxymethylthio 2-methylaminosulfonyl)-ethylthio and 2-dimethylaminophosphonyl)ethylthio.

Preferably R^3 and R^4 together with the carbon atoms to which they are attached form a ring of formula:



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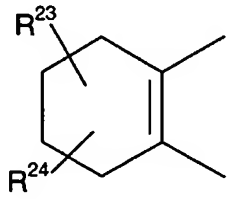

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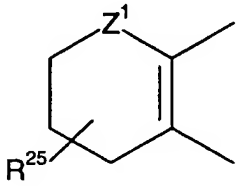

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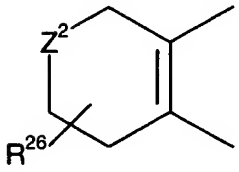

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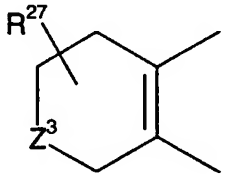

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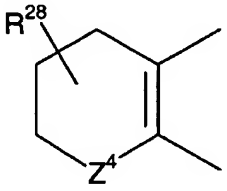

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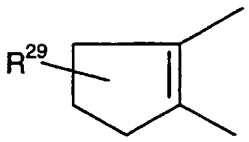

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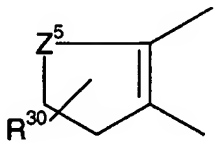

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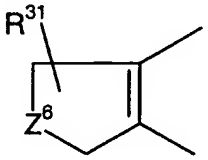

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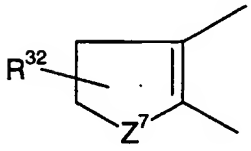

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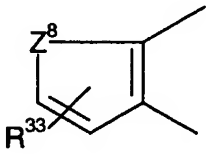

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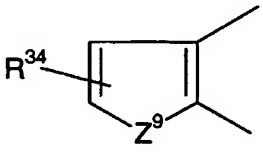

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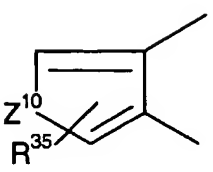

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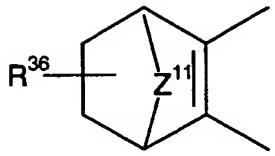

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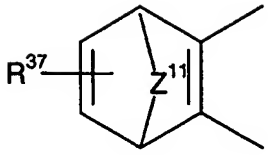

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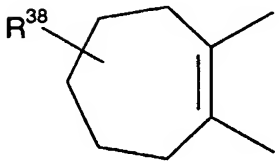


p

in which:

Z^1, Z^2, Z^3, Z^4, Z^5, Z^6, Z^7, Z^8, Z^9 and Z^{10} are each selected independently from O, NR^{41}, S, SO and SO_2;

Z^{11} represents O, S, CH_2 or CH_2CH_2;

R^{21} and R^{22} each independently represents a hydrogen atom, a halogen atom, a nitro group, a cyano group, a (1-4C)alkyl group, a halo(1-4C)alkyl group, or a group of formula $-X^4-R^{51}$ in which X^4 represents O, S, SO, SO_2, NR^{52}, CO, COO, OCO, CONH, NHCO, SO_2NH, or $NHSO_2$ and R^{51} represents a hydrogen atom, a (1-4C)alkyl group, a phenyl group or a phenyl(1-4C)alkyl group in which any phenyl group is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a (1-4C)alkoxy group;

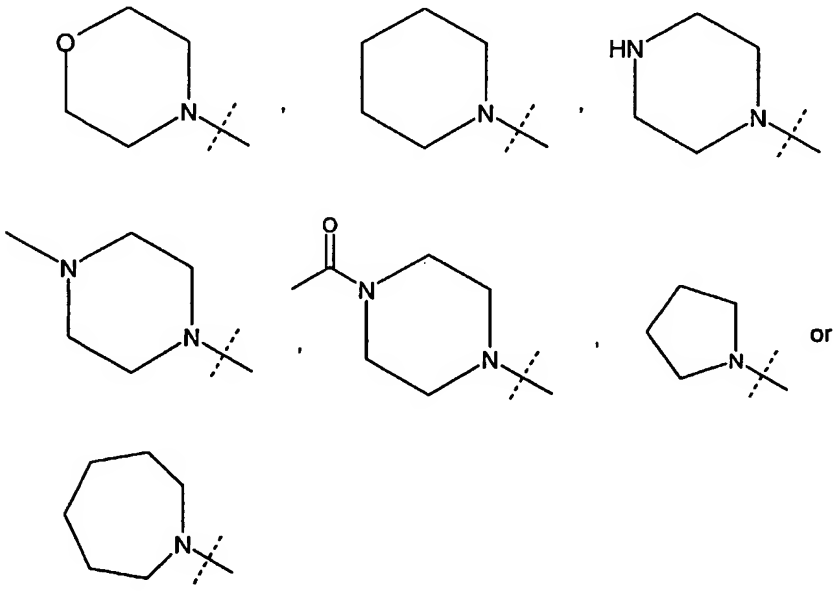
R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{36}, R^{37} and R^{38} each independently represents a hydrogen atom, an oxo group, a halogen atom, a (1-4C)alkyl group, (1-4C)alkoxy, a halo(1-4C)alkyl group, an aryl(1-4C)alkyl group, a (1-4C)alkoxy(1-4C)alkyl group, a (1-4C)alkylthio group, a (1-4C)alkylsulfinyl group, a (1-4C)alkylsulfonyl group or a (1-4C)alkanoyl group;

R^{33}, R^{34} and R^{35} each independently represents a hydrogen atom, a halogen atom, a (1-4C)alkyl group or a (1-4C)alkoxy group;

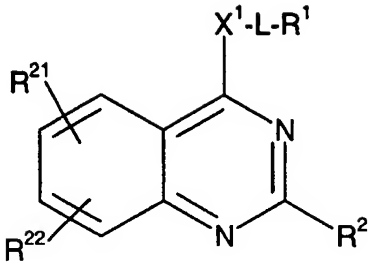
R^{41} represents a (1-6C)alkyl group or a group of formula Y-R^a in which Y represents CO, COO or CONH and R^a represents (1-4C)alkyl, phenyl(1-4C)alkyl, phenyl(2-4C)alkenyl, (3-10C)cycloalkyl, or, when Y is CO, morpholino; and

R^{52} represents a hydrogen atom, a (1-4C)alkyl group or a phenyl(1-4C)alkyl group.

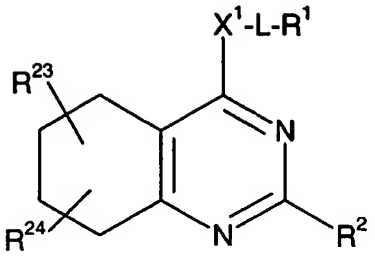
When X^4 represents NR^{52}, R^{51} represents a hydrogen atom, a (1-4C)alkyl group, a phenyl group or a phenyl(1-4C)alkyl group in which any phenyl group is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a (1-4C)alkoxy group; and R^{52} represents a hydrogen atom, a (1-4C)alkyl group or a phenyl(1-4C)alkyl group; or R^{51} and R^{52} together with the nitrogen atom to which they are attached form rings of the following structures:



Examples of groups of compounds of formula I of particular interest include compounds of formula



Ia



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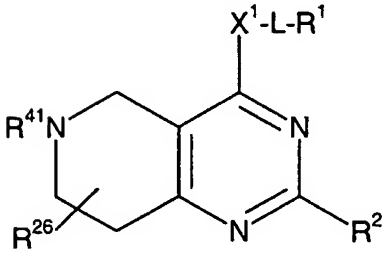
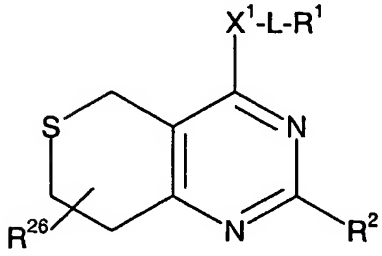
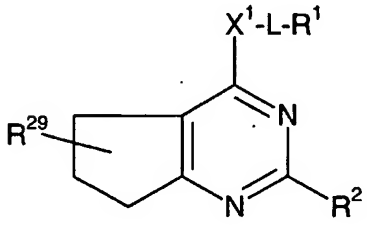


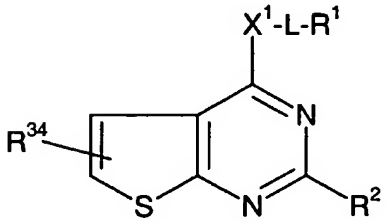
Id1



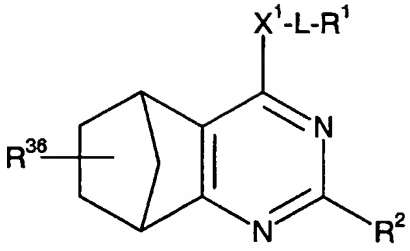
Id2



Ig



Ii1



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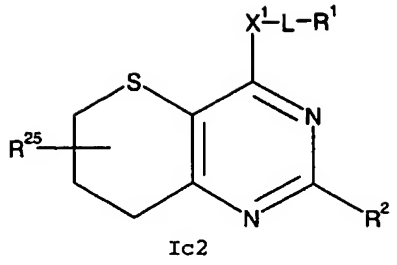
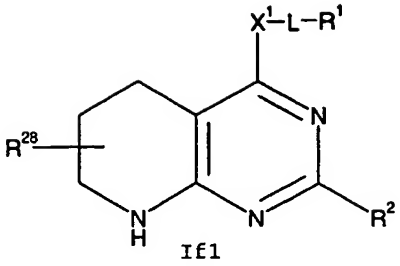


Ic2



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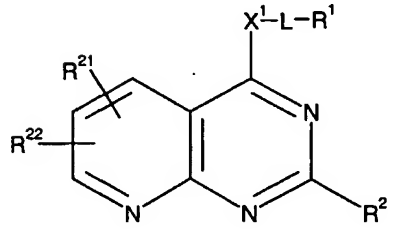

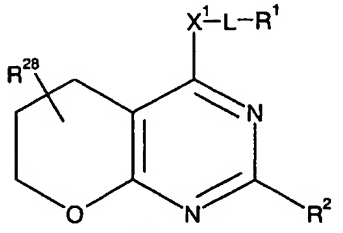

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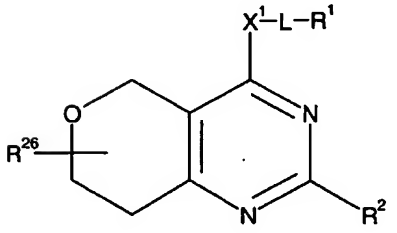
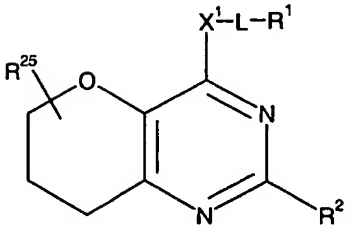


Id3



Ic2

Examples of values for R^{21} and R^{22} are a hydrogen atom, a fluorine atom, a chlorine atom, a nitro group, a hydroxyl group, a carboxyl group, a methyl group and a methoxy group.

An example of a value for each of R^{23} and R^{24} is hydrogen. Another example of a value for R^{23} is oxo.

Examples of values for R^{41} are methyl, benzyl, 2-methyl-3-prop-2-enoyl, cyclopentylcarbonyl, cyclohexycarbonyl, morpholinocarbonyl, cyclohexylaminocarbonyl, adamantylaminocarbonyl and benzylaminocarbonyl, benzyloxycarbonyl.

An example of a value for R^{26} is hydrogen.

An example of a value for R^{29} is hydrogen.

Examples of values for R^{34} are hydrogen, chlorine, methyl and ethyl.

An example of a value for R^{36} is hydrogen.

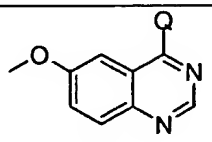
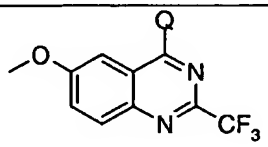
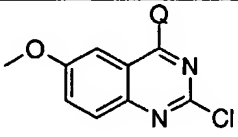
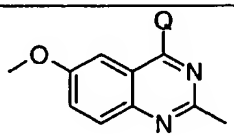
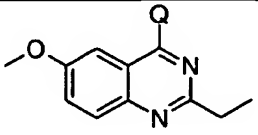
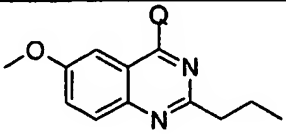
An example of a value for R^{37} is hydrogen.

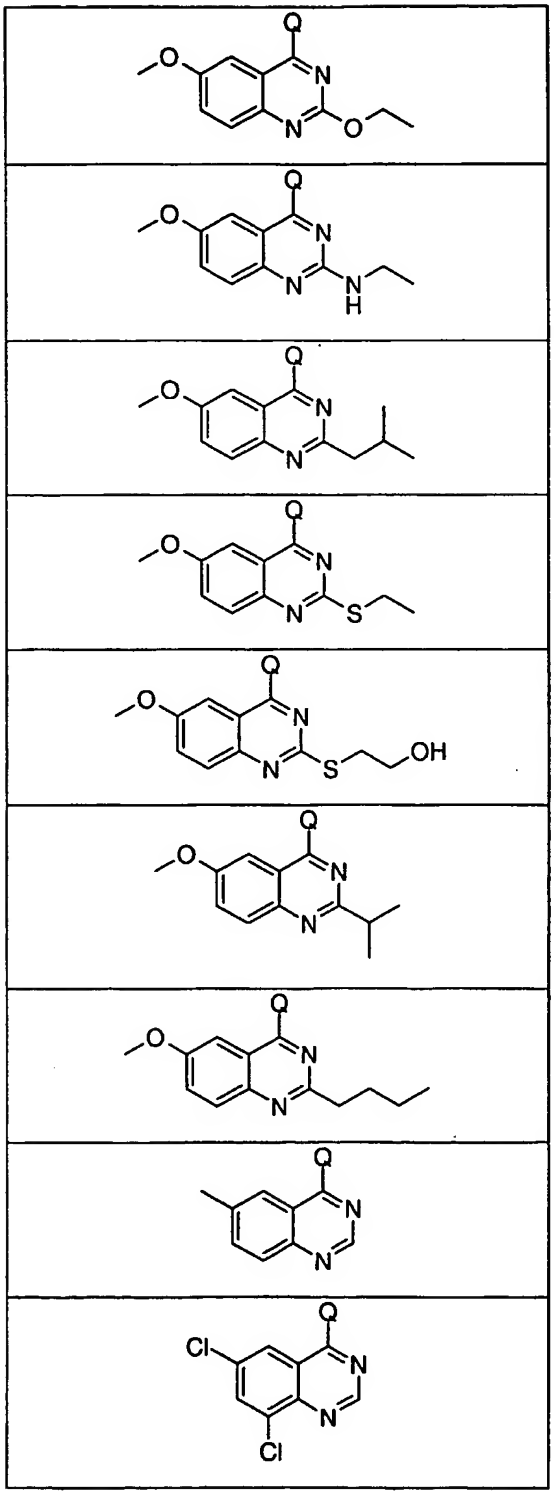
An example of a value for R^{38} is hydrogen.

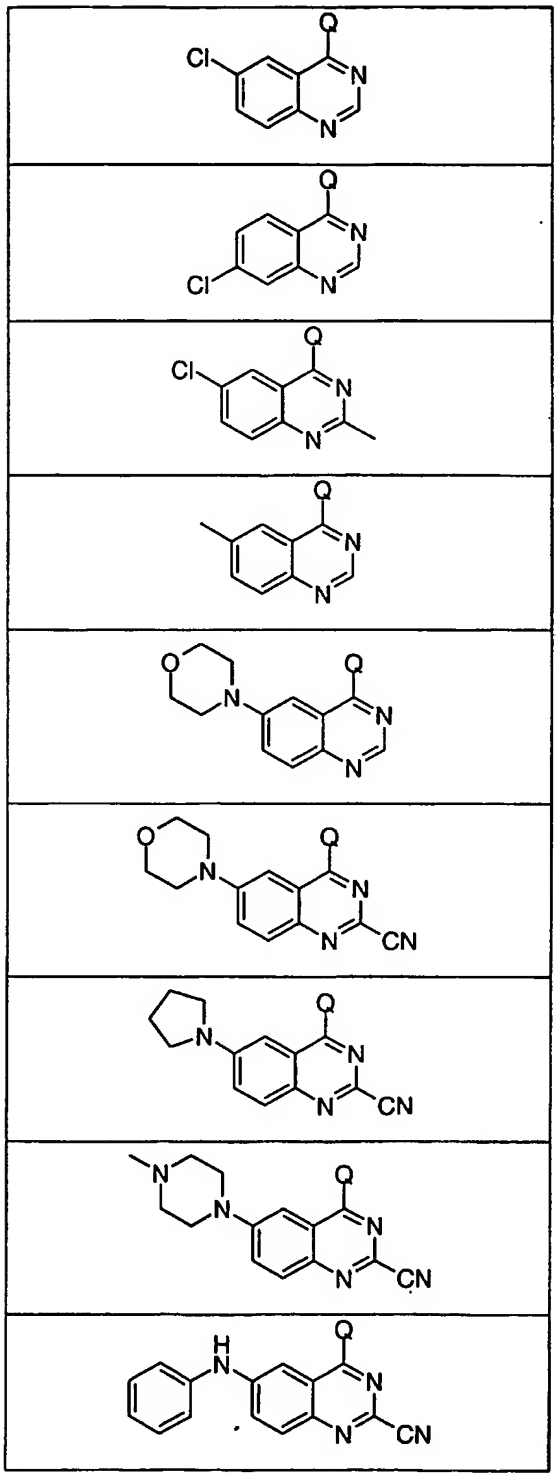
Especially preferred compounds included within the scope of formula I are set forth in Table 1 wherein Q represents

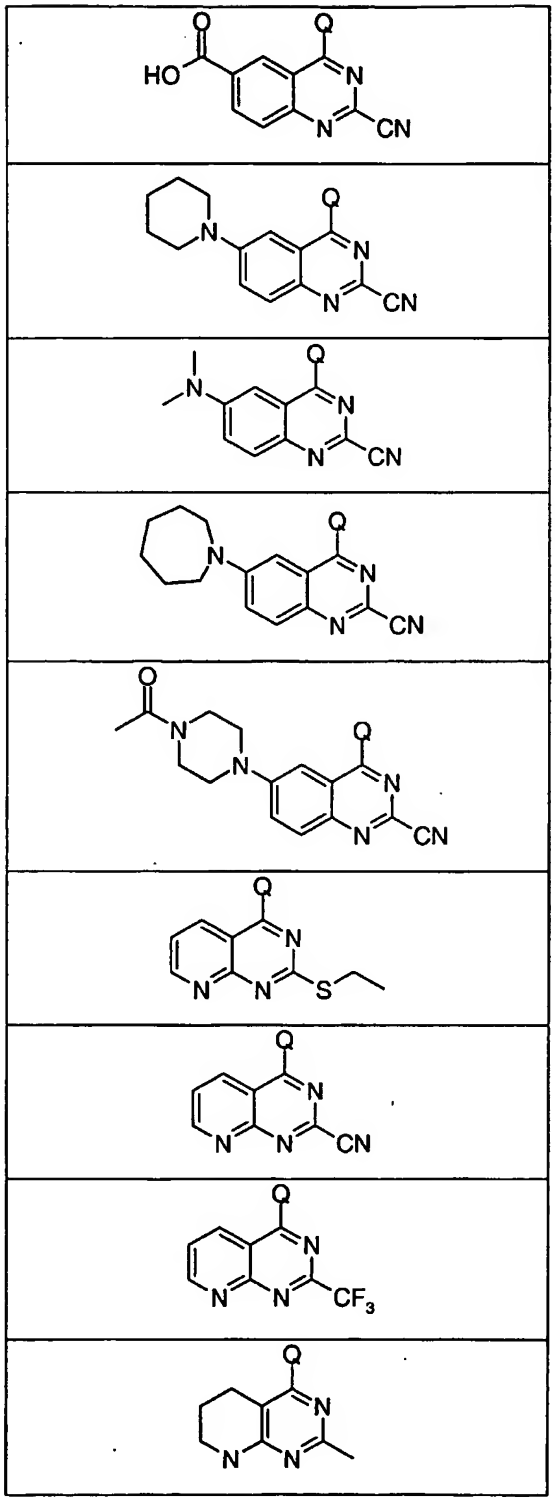
-NH-L-R^1.

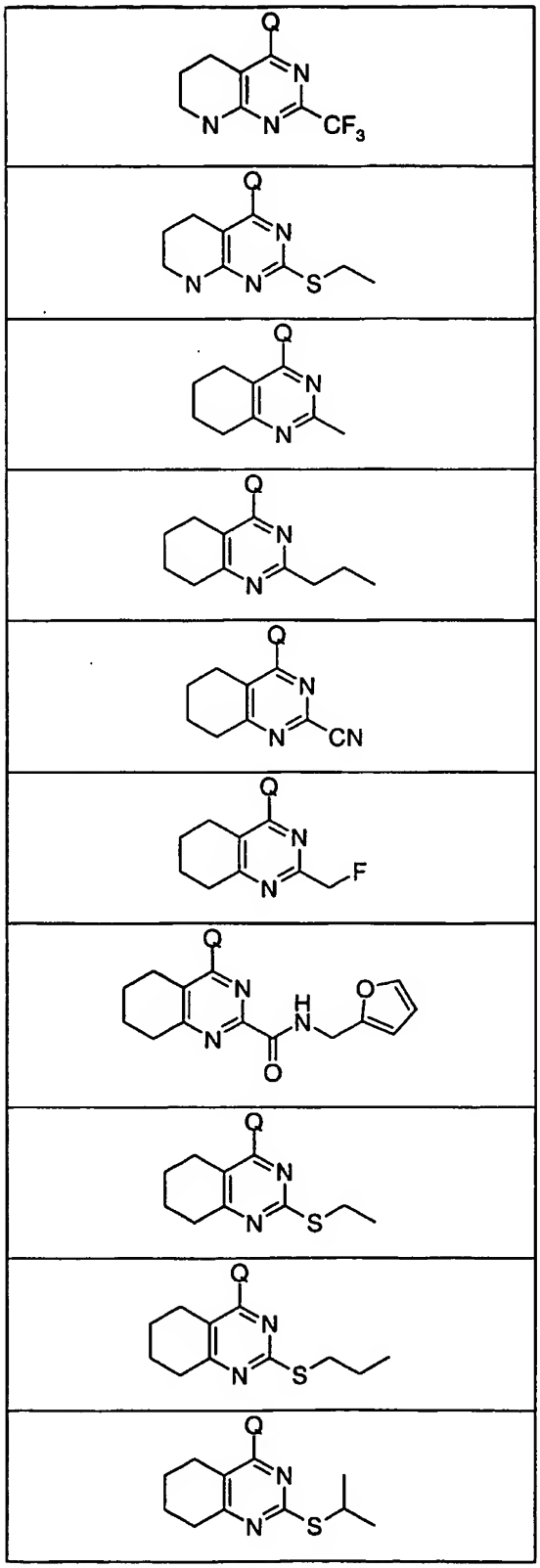
Table I.

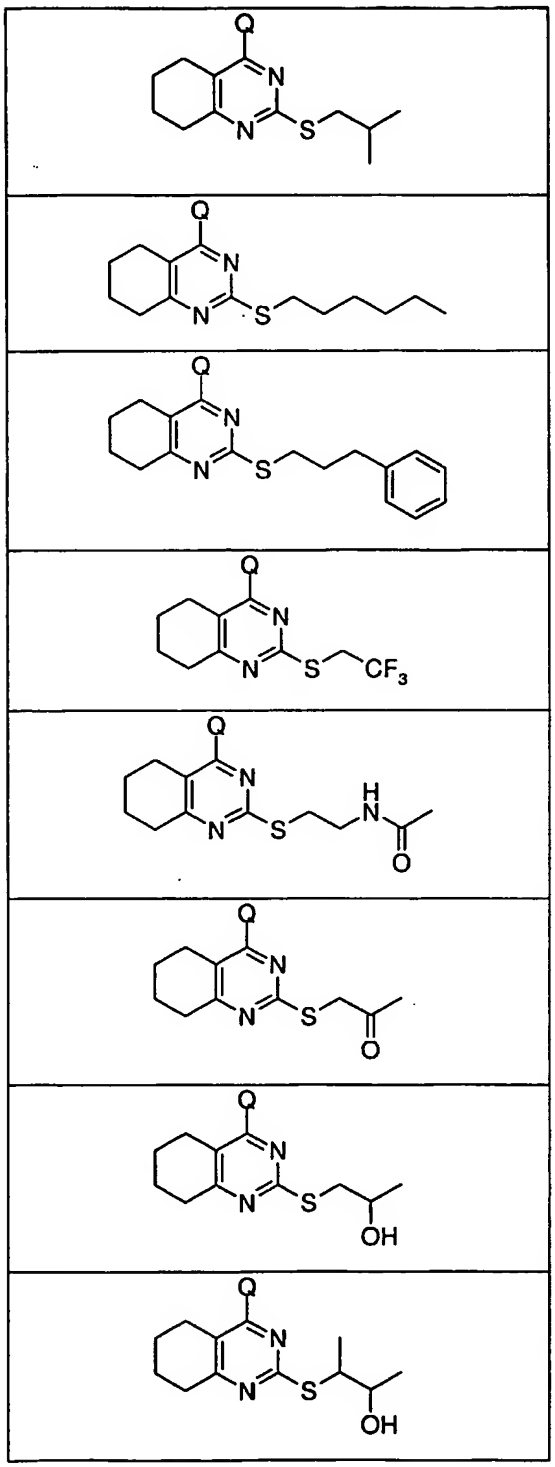







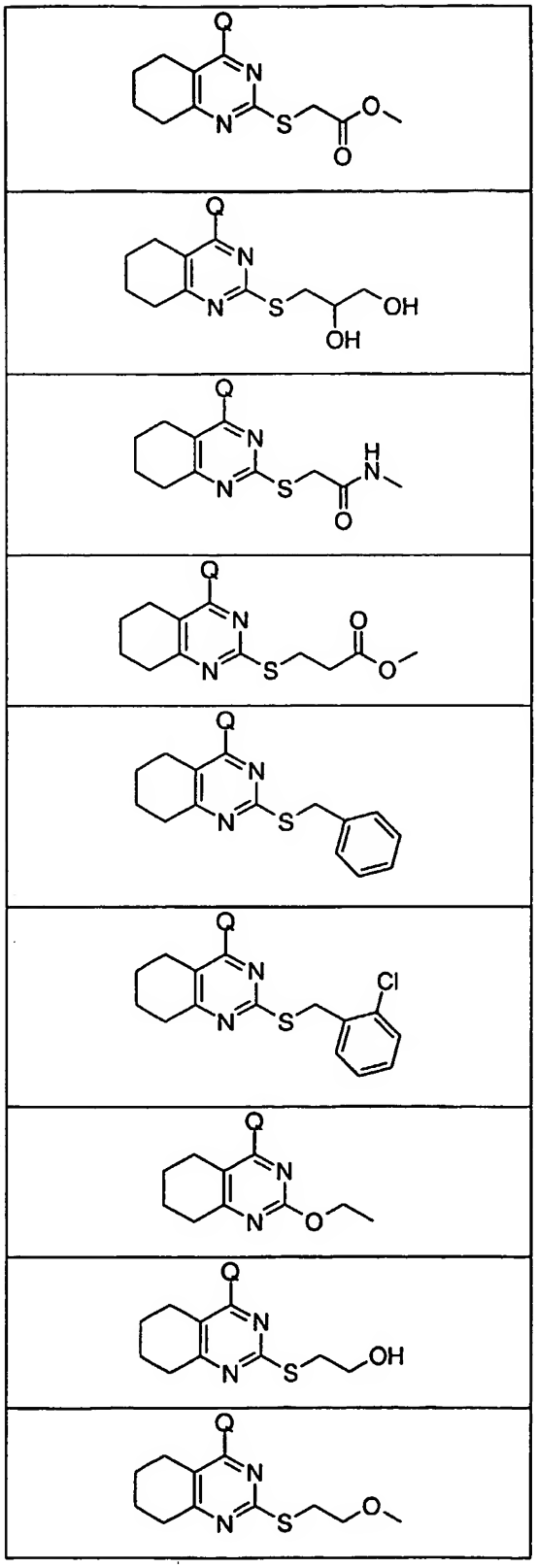


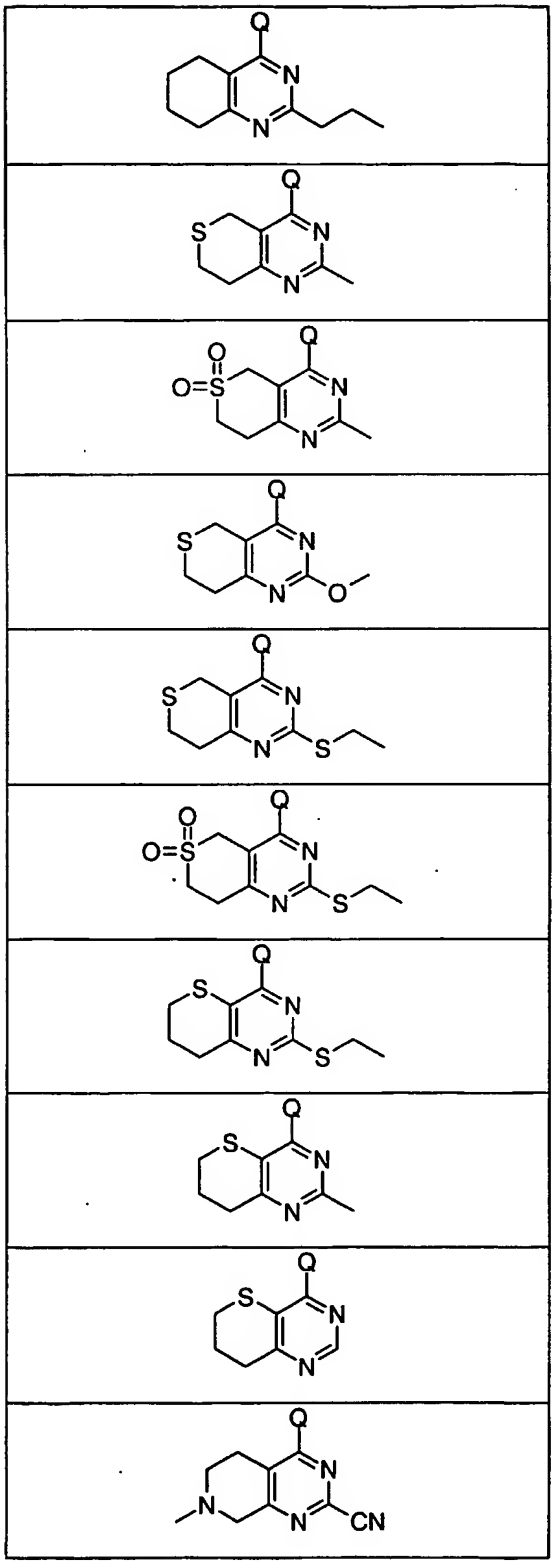


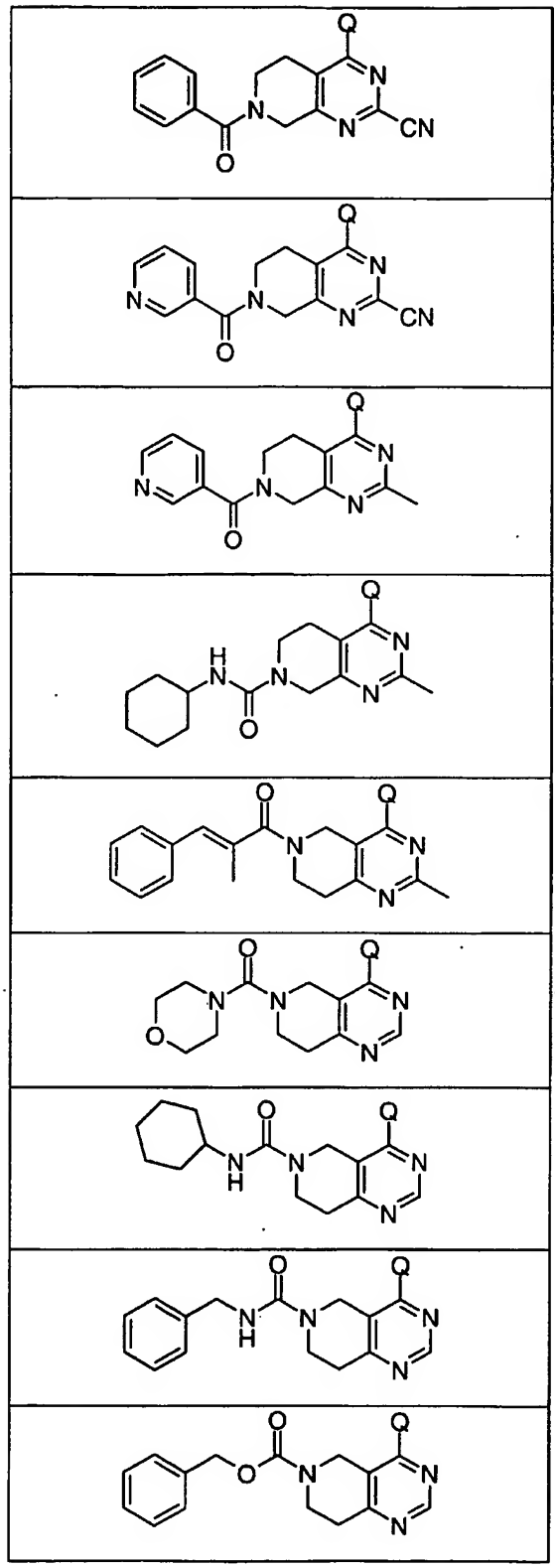


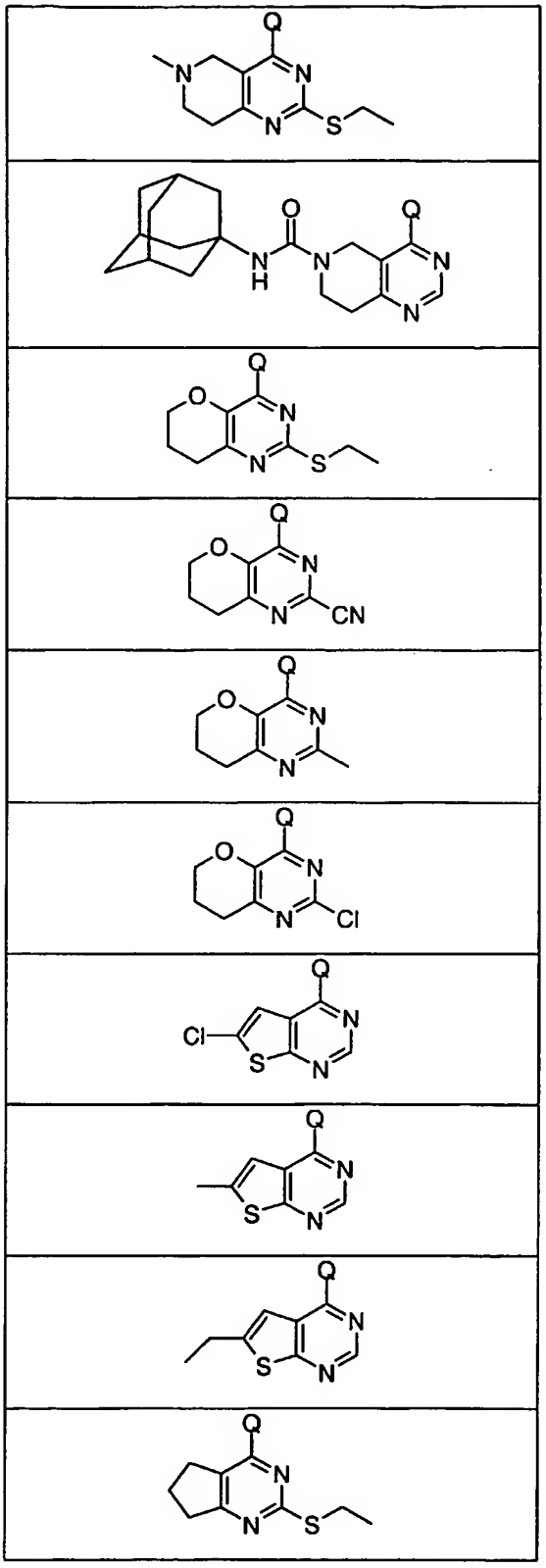


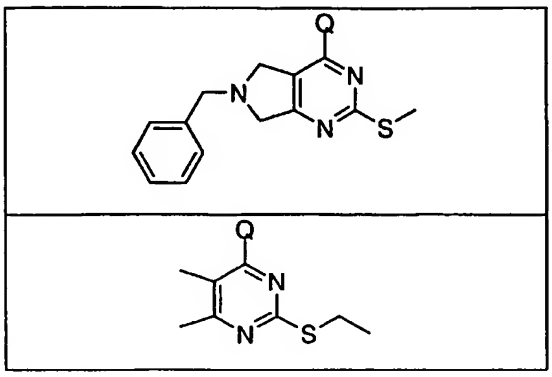












The present invention includes pharmaceutically acceptable salts of the formula I compounds. These salts can exist in conjunction with the acidic or basic portion of the molecule and can exist as acid addition, primary, secondary, tertiary, or quaternary ammonium, alkali metal, or alkaline earth metal salts. Generally, the acid addition salts are prepared by the reaction of an acid with a compound of formula I. The alkali metal and alkaline earth metal salts are generally prepared by the reaction of the hydroxide form of the desired metal salt with a compound of formula I.

Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydriodic, sulfuric, and phosphoric acid, as well as organic acids such as *para*-toluenesulfonic, methanesulfonic, oxalic, *para*-bromophenylsulfonic, carbonic, succinic, citric, benzoic, and acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, ammonium, monohydrogenphosphate, dihydrogenphosphate, *meta*-phosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propiolate, oxalate, malonate, succinate,

suberate, sebacate, fumarate, hippurate, butyne-1,4-dioate, hexane-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, α-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, magnesium, tetramethylammonium, potassium, trimethylammonium, sodium, methylammonium, calcium, and the like salts.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. It is further understood that the above salts may form hydrates or exist in a substantially anhydrous form.

As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers". The terms "racemate", "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers.

The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as

compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee", which is found using the following equation:

$$ee = \frac{E^1 - E^2}{E^1 + E^2} \times 100$$

wherein E^1 is the amount of the first enantiomer and E^2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 70:30 is achieved, the ee with respect to the first enantiomer is 40%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. An ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most especially preferred. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and procedures, such as gas or high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is well within the knowledge of one of ordinary skill in the art.

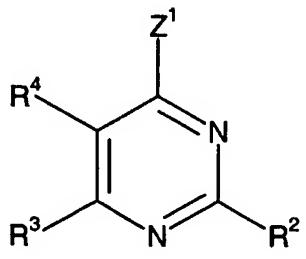
In addition, the specific stereoisomers and enantiomers of compounds of formula I can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen," Stereochemistry of Organic Compounds", (Wiley-Interscience 1994), and European Patent Application No. EP-A-838448, published April 29, 1998. Examples of resolutions include recrystallization techniques or chiral chromatography.

Some of the compounds of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

The compounds of formula I may be prepared by a process which comprises

(a) reacting a compound of formula



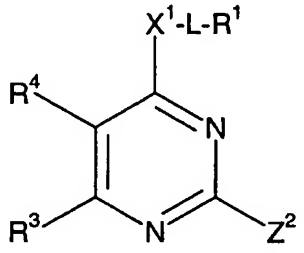
II

in which Z^1 represents a leaving atom or group,
with a compound of formula

$$R^1\text{-}L\text{-}X^1H$$

III

(b) for a compound of formula I in which R2 represents $X^2\text{-}R^5$, reacting a compound of formula



IV

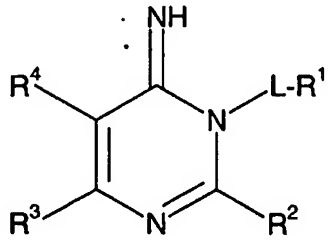
in which Z^2 represents a leaving atom or group
with a compound of formula

$$HX^2\text{-}R^5$$

V

or a base salt thereof;

(c) for a compound of formula I in which X^1 represents NH, rearranging a compound of formula



VI

followed where desired by forming a pharmaceutically acceptable salt.

In process step (a), the leaving atom or group represented by Z^1 may be, for example, a halogen atom such as a chlorine atom. The reaction is conveniently performed in the presence of a base, for example an alkali metal

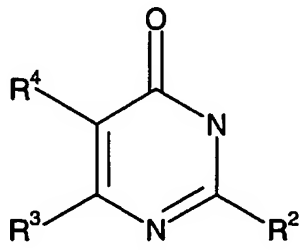
carbonate, such as potassium carbonate or a tertiary amine such as triethylamine or diisopropylethylamine, or poly(4-vinylpyridine). The reaction is conveniently conducted at a temperature in the range of from 0 to 120ºC. Convenient solvents include alcohols, such as ethanol and amides such as N,N-dimethylformamide or N-methylpyrrolidinone.

In process step (b), the leaving atom or group represented by Z^2 may be, for example, a halogen atom such as a chlorine atom or an organosulfonyl group such as methanesulfonyl. The reaction is conveniently performed in the presence of a base, for example an alkali metal alkoxide such as potassium t-butoxide. Alternatively, a base salt of the compound of formula V may be used, for example an alkali metal salt such as a sodium or potassium salt. The reaction is conveniently conducted at a temperature in the range of from 0 to 100ºC. Convenient solvents include amides such as N,N-dimethylformamide.

The rearrangement according to process step (c) is conveniently effected in the presence of an anionic ion exchange resin, such as 550A-OH and at a temperature of from 0 to 120ºC. Convenient solvents include mixtures of dimethylformamide and alcohols, such as isopropanol.

Pharmaceutically acceptable salts of compounds of formula I may be prepared by conventional methods, for example by reaction with an appropriate acid of base.

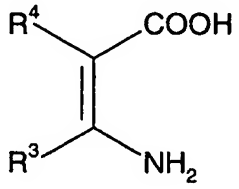
Compounds of formula II may be prepared by reacting a compound of formula



XX

with an appropriate activating agent, for example a halogenating agent such as phosphorous oxychloride. The reaction is conveniently performed at a temperature in the range of from 20 to 150ºC.

Compounds of formula XX may be prepared by reacting a compound of formula



XXI

with a compound of formula

H_2NCOR^2

XXII

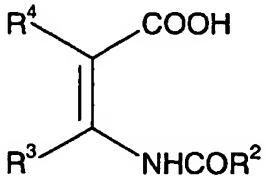
The reaction is conveniently performed at an elevated temperature, for example in the range of from 100 to 220ºC.

Alternatively, compounds of formula XX may be prepared by reacting a compound of formula XXI with a compound of formula

$HOOCR^2$

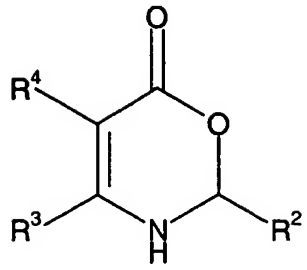
XXIII

or a reactive derivative thereof to afford a compound of formula



XXIV

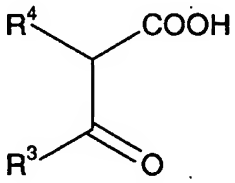
followed by reaction of the compound of formula XXIV with ethyl chloroformate in the presence of a base, such as triethylamine, to afford a compound of formula



XXV

The compound of formula XXV is then reacted with concentrated ammonia to afford the compound of formula XX.

Compounds of formula XX may also be prepared by reacting a compound of formula



XXVI

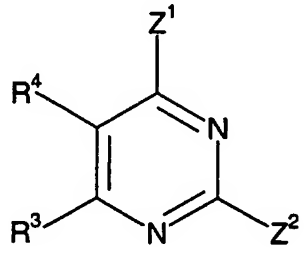
or an ester thereof, such as a methyl ester, with a compound of formula

$R^2C(=NH)NH_2$

XXVII

or an acid addition salt thereof, such as a hydrochloride or hydrobromide. Convenient solvents include alcohols, such as ethanol. The reaction is conveniently performed at a temperature of from 0 to 100°C.

Compounds of formula IV may be prepared by reacting a compound of formula



XXVIII

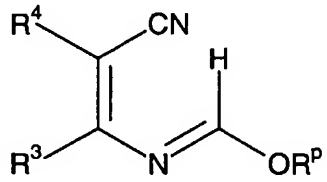
with a compound of formula III, following the method of step (a).

Compounds of formula XXVIII may be prepared by reacting a compound of formula XXI with a compound of formula

H_2NCONH_2

to afford a compound of formula XXVIII in which Z^1 and Z^2 each represents hydroxyl, followed by reacting this with an appropriate activating agent, for example a halogenating agent such as phosphorous oxychloride.

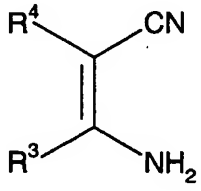
Compounds of formula VI may be prepared by reacting a compound of formula



XXIX

in which R^p represents an alkyl group, such as methyl, with a compound of formula III in which X^1 represents NH. Convenient solvents include alcohols, such as ethanol. The temperature is conveniently in the range of from 0 to 100ºC.

Compounds of formula XXIX may be prepared by reacting a compound of formula



XXX

with a trialkylorthoformate, such as trimethylorthoformate. The reaction is conveniently performed in the presence of a cationic ion exchange resin, such as 50wx8-100, and at a temperature in the range of from 0 to 120ºC.

Many of the compounds of formula I and the intermediates useful in the preparation of the compounds of

formula I, for example compounds of formula II, IV and VI, are believed to be novel. According to another aspect, the present invention provides the novel compounds of formula I disclosed herein and the novel intermediates disclosed herein. The present invention also provides a process for preparing a novel compound of formula I as described hereinabove.

The biological activity of the compounds of the present invention may be evaluated by employing a phosphoinositide hydrolysis assay or a calcium mobilization assay. As mentioned supra, "metabotropic" glutamate receptors are G-protein, or secondary messenger-linked, receptors. As such, these receptors are linked to multiple second messenger systems which enhance phosphoinositide hydrolysis, activation of phospholipase D, increases or decreases in c-AMP formation, and changes in ion channel function. Schoepp and Conn, *Trends in Pharmacol. Sci.*, 14, 13 (1993). A general description of the phosphoinositide hydrolysis assay is given as follows:

(a) Cell cultures:

mGluR1 receptor-expressing cell lines are cultured in DMEM supplemented with 5% heat inactivated fetal calf serum, sodium pyruvate (1mM), glutamine (1mM), penicillin (100U/mL), streptomycin (100mg/mL), HEPES (10mM), geneticin G418 (0.5mg/mL) and hygromycin B (0.2mg/mL). Confluent cultures are passaged weekly.

(b) Phosphoinositide Hydrolysis Assay:

Transfected cells are seeded into 24 well culture plates at 2.5 x 10^5 cells per well in medium containing no added glutamine and cultured at 37°C in a humidified atmosphere of 5% CO_2 in air. After 24hr, the cells are labeled with [3H]-inositol (4uCi/mL) for a further 20hr. Cells are washed in assay medium containing HEPES (10mM), inositol (10mM) and lithium chloride (10mM). Test compounds are added to the cell cultures 20 min prior to the addition of quisqualate and then the culture is further incubated in the presence of agonist for 60 min. The reaction is terminated by replacing the medium with acetone:methanol (1:1) and then incubating the cultures on ice for 20 min. Separation of the [3H]-inositol phosphates is carried out by Sep -Pak Accell Plus QMA ion exchange chromatography (Waters, Millipore Ltd., UK) according to the method described by Maslanski and Busa (*Methods in Inositide Research;* ed. Irvine, R.F. pp. 113-126; New York, Raven Press Ltd. 1990). The [3H]-inositol monophosphate (INS P1) fraction is eluted with 0.1M triethyl ammonium bicarbonate buffer and radioactivity measured by liquid scintillation counting. Following the measurement of radioactivity for each fraction eluted, IC_{50} calculations are made for each test compound examined. The compounds exemplified herein generated IC_{50} values equal to or less than 10 μM in the phosphoinositide assay herein described.

Alternatively, the biological activity of the compounds of the present invention can be determined employing an assay which monitors intracellular calcium ion concentration in response to metabotropic glutamate receptor activation. As stated supra, activation of G-protein coupled receptors triggers a sequence of events which contribute to alterations in intracellular calcium concentration. By monitoring alterations in calcium ion concentration in response to metabotropic glutamate receptor activation, one can identify compounds functional as metabotropic glutamate receptor antagonists. A general description of a calcium flux assay which can be employed to determine the biological activity of the compounds of the present invention is given as follows:

(a) Plate Preparation:

Plates containing cells expressing mGluR1 are prepared using standard methods well known to those of skill in the art. Reagent plates are prepared containing 160µl/well of buffer (1% DMSO or compound in 1%DMSO buffer) and additional plates are prepared containing 260µl/well of 10M glutamate in assay buffer.

(b) Calcium Flux Assay:

Media is removed from the plates containing the cells expressing mGluR1 using a hand held aspirator or standard plate washer. 50µl of 10µM Fluo3 Dye is added to each well which in turn will emit fluorescence upon binding to calcium ions. Cells are incubated at room temperature for approximately 90 minutes to allow the Fluo3 Dye to load into the cells. The dye is then aspirated and replaced with 50µl of buffer. The plates are placed in a fluorescent light imaging plate reader (FLIPR) such that the plate containing

the buffer or compound is to the right of the cell plate, while the plate containing the glutamate is placed to the left of the cell plate. The FLIPR is programmed to take background fluorescence readings for 10 seconds then add buffer or compound to the cell plates. After 3 minutes, the FLIPR adds 100µl of 10µM glutamate to mobilize cellular calcium ion stores and fluorescence is measured for about a minute. Fluorescence values for cells containing buffer are compared relative to cells containing mGluR1 antagonist compound. Percent inhibition of mGluR1 elicited calcium ion influx, as indexed by fluorescence, is calculated for each compound.

The ability of test compounds to treat forms of pain may be demonstrated by activity in one or more standard tests, such as the formalin test, the Chung neuropathic pain model and the carrageenan test of inflammatory pain.

1) formalin test

Male Sprague-Dawley rats (200-250g; Charles River, Portage, MI) are housed in group cages and maintained in a constant temperature and a 12h light/12h dark cycle 4-7 days before the studies are performed. Animals have free access to food and water at all times prior to the day of the experiment.

Drugs or vehicles are administered intraperitoneally (i.p.) or orally (p.o.) by gavage in a volume of 1 mL/kg.

The test is performed in custom-made Plexiglas® boxes 25x25x20x cm in size (according to Shibata *et al.*, Pain 38; 347-352, 1989, Wheeler-Aceto *et al.*, Pain, 40; 229-238, 1990). A mirror placed at the back of the cage allows the unhindered observation of the formalin injected paw. Rats are acclimated individually in the cubicles at least 1 hour prior to the experiment. All testing is conducted between 08:00 and 14:00 h and the testing room temperature is

maintained at 21-23°C. Test compounds are administered 30 minutes prior to the formalin injection. Formalin (50 µl of a 5% solution in saline) is injected subcutaneously into the dorsal lateral surface of the right hind paw with a 27 gauge needle. Observation starts immediately after the formalin injection. Formalin-induced pain is quantified by recording in 5 minute intervals the number of formalin injected paw licking events and the number of seconds each licking event lasts. These recordings are made for 50 minutes after the formalin injection.

Different scoring parameters have been reported for the formalin test. The total time spent licking and biting the injected paw was demonstrated to be most relevant (Coderre *et al.*, *Eur. J. Neurosci.* 6; 1328-1334, 1993; Abbott *et al.*, Pain, 60; 91-102, 1995) and is chosen for the testing score. The early phase score is the sum of time spent licking in seconds from time 0 to 5 minutes. The late phase is scored in 5 minute blocks from 15 minutes to 40 minutes and is expressed accordingly or also by adding the total number of seconds spent licking from minute 15 to minute 40 of the observation period. Data are presented as means with standard errors of means (± SEM). Data are evaluated by one-way analysis of variance (ANOVA) and the appropriate contrasts analyzed by Dunnett "t" test for two sided comparisons. Differences are considered to be significant if the P-value was less than 0.05 and indicated by asterisk. Statistics were determined at the 5 minute time point and at 5 minute intervals between 15 and 40 minutes. Where data are expressed as total amount of time spent licking in the late phase, statistics are performed on the total time spent licking as well and are indicated accordingly.

The following compounds of formula I have been found to show activity in this test:

4-(Bicyclo[2.2.1]hept-2-ylamino)-8-chloroquinazoline hydrochloride (A);
4-(Bicyclo[2.2.1]hept-2-ylamino)-6-chloroquinazoline hydrochloride (B);
4-(4-Methoxyphenylamino)-6-methoxyquinazoline hydrochloride (C);
4-[2-(2,6-Dichlorobenzylthio)ethylamino]-6-methoxy-quinazoline (D);
2-(2-Hydroxyethylthio)-4-(bicyclo[2.2.1]hept-2-ylamino)-6-chloroquinazoline hydrochloride (E);
2-(2-Hydroxyethylthio)-4-(4-methoxyphenylamino)-6-methoxyquinazoline hydrochloride (F);
N-(2-((2,6-dichlorobenzyl)thio)ethyl)-2-methyl-5,6,7,8-tetrahydroquinazolin-4-amine, hydrochloride (G); and
N-(2,3-dihydro-*1H*-inden-2-yl)-2-(2-hydroxyethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride(H).

2. Chung neuropathic pain model

The following compound of formula I has been found to show activity in this test:
4-(Bicyclo[2.2.1]hept-2-ylamino)-6-chloroquinazoline hydrochloride (B)

3. Carrageenan test of inflammatory pain

The following compounds of formula I have been found to show activity in this test:
4-(Bicyclo[2.2.1]hept-2-ylamino)-6-chloroquinazoline hydrochloride (B)
4-(4-Methoxyphenylamino)-6-methoxyquinazoline hydrochloride (C); and
N-(2,3-dihydro-*1H*-inden-2-yl)-2-(2-hydroxyethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride(H).

According to one preferred aspect therefore, the present invention provides a method of treating pain, which

comprises administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinabove.

The ability of test compounds to treat migraine may be demonstrated in the following test.

1. Animal Model of Dural Protein Extravasation

Harlan Sprague-Dawley rats (225-325 g) or guinea pigs from Charles River Laboratories (225-325 g) are anesthetized with sodium pentobarbital intraperitoneally (65 mg/kg or 45 mg/kg respectively) and placed in a stereotaxic frame (David Kopf Instruments) with the incisor bar set at -3.5 mm for rats or -4.0 mm for guinea pigs. Following a midline sagital scalp incision, two pairs of bilateral holes are drilled through the skull (6 mm posterially, 2.0 and 4.0 mm laterally in rats; 4 mm posteriorly and 3.2 and 5.2 mm laterally in guinea pigs, all coordinates referenced to bregma). Pairs of stainless steel stimulating electrodes, insulated except at the tips (Rhodes Medical Systems, Inc.), are lowered through the holes in both hemispheres to a depth of 9 mm (rats) or 10.5 mm (guinea pigs) from dura.

The femoral vein is exposed and a dose of the test compound is injected intravenously (i.v.) at a dosing volume of 1mL/Kg or, in the alternative, test compound is administered orally (p.o.) via gavage at a volume of 2.0mL/Kg. Approximately 7 minutes post i.v. injection, a 50 mg/Kg dose of Evans Blue, a fluorescent dye, is also injected intravenously. The Evans Blue complexed with proteins in the blood and functions as a marker for protein extravasation. Exactly 10 minutes post-injection of the test compound, the left trigeminal ganglion is stimulated for 3 minutes at a current intensity of 1.0 mA (5 Hz, 4 msec duration) with a Model 273 potentiostat/ galvanostat (EG&G Princeton Applied Research).

Fifteen minutes following stimulation, the animals are killed and exsanguinated with 20 mL of saline. The top of

the skull is removed to facilitate the collection of the dural membranes. The membrane samples are removed from both hemispheres, rinsed with water, and spread flat on microscopic slides. Once dried, the tissues are coverslipped with a 70% glycerol/water solution.

A fluorescence microscope (Zeiss) equipped with a grating monchromator and a spectrophotometer is used to quantify the amount of Evans Blue dye in each sample. An excitation wavelength of approximately 535 nm is utilized and the emission intensity at 600 nm is determined. The microscope is equipped with a motorized stage and also interfaced with a personal computer. This facilitates the computer-controlled movement of the stage with fluorescence measurements at 25 points (500 mm steps) on each dural sample. The mean and standard deviation of the measurements are determined by the computer.

The extravasation induced by the electrical stimulation of the trigeminal ganglion is an ipsilateral effect (i.e. occurs only on the side of the dura in which the trigeminal ganglion is stimulated). This allows the other (unstimulated) half of the dura to be used as a control. The ratio of the amount of extravasation in the dura from the stimulated side, over the amount of extravasation in the unstimulated side, is calculated. Control animals dosed with only saline, yield a ratio of approximately 2.0 in rats and approximately 1.8 in guinea pigs. In contrast, a compound which effectively prevented the extravasation in the dura from the stimulated side would yield a ratio of approximately 1.0.

Dose-response curves are generated for each of the panel of compounds and the dose that inhibits the extravasation by 50% (ID_{50}) or 100% (ID_{100}) is approximated.

The following compounds of formula I have been found to show activity in this test:

4-(Bicyclo[2.2.1]hept-2-ylamino)-8-chloroquinazoline hydrochloride (A);

4-(Bicyclo[2.2.1]hept-2-ylamino)-6-chloroquinazoline hydrochloride (B);

4-(4-Methoxyphenylamino)-6-methoxyquinazoline hydrochloride (C);

4-[2-(2,6-Dichlorobenzylthio)ethylamino]-6-methoxy-quinazoline (D);

2-(2-Hydroxyethylthio)-4-(bicyclo[2.2.1]hept-2-ylamino)-6-chloroquinazoline hydrochloride (E);

2-(2-Hydroxyethylthio)-4-(4-methoxyphenylamino)-6-methoxyquinazoline hydrochloride (F);

N-(2-((2,6-dichlorobenzyl)thio)ethyl)-2-methyl-5,6,7,8-tetrahydroquinazolin-4-amine, hydrochloride (G); and

N-(2,3-dihydro-*1H*-inden-2-yl)-2-(2-hydroxyethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride(H).

According to one preferred aspect therefore, the present invention provides a method of treating migraine, which comprises administering to a patient in need thereof an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinabove.

The compounds (A) to (H) above have all been found to be selective mGluR1 antagonists. In particular, all of the compounds have been found to exhibit at least 10 fold selectivity for mGluR1 over mGluR5 in the test described hereinabove.

Test Compound	mGluR1 IC_{50} PI nM	mGluR5 IC_{50} PI nM
A	1895	>100000
B	400	13000
C	96	>3000
D	46	4133
E	44	>4000
F	11	>1000
G	7	~10000
H	<1	>10000

It is believed that the present application contains the first disclosure that a compound which is a selective mGluR1 antagonist is useful for the treatment of migraine.

According to another aspect, therefore, the present invention provides a method of treating migraine, which comprises administering to a patient in need of treatment an effective amount of a selective mGluR1 antagonist.

The selective mGluR1 antagonist is preferably at least 10 fold selective for mGluR1 over mGluR5, more preferably at least 100 fold selective.

The compounds of the present invention are preferably formulated prior to administration. Therefore, another aspect of the present invention is a pharmaceutical formulation comprising a compound of formula I or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier. The present pharmaceutical formulations are prepared by known procedures using well-known and readily available ingredients. In making the formulations of the present invention, the active

ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. The compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments containing, for example, up to 10% by weight of active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable carriers include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum, acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propyl hydroxybenzoates, talc, magnesium stearate, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents. Formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The formulations are preferably formulated in a unit dosage form, each dosage containing from about 5 mg to about 500 mg, more preferably about 25 mg to about 300 mg of the active ingredient. The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to

produce the desired therapeutic effect, in association with a suitable pharmaceutically acceptable carrier.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

Tablets each containing 60 mg of active ingredient are made as follows:

Active Ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50¡C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

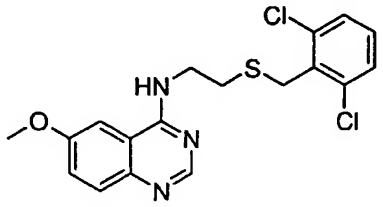
The following examples further illustrate the invention and represent typical syntheses of the compounds of formula I as described generally above. The reagents and starting materials are readily available to one of ordinary skill in the art. As used herein, the following terms have the

meanings indicated: "Flash 40S", "Flash 40M", and "Flash 40L" refer to flash chromatography cartridges with the corresponding specifications; 7 X 4 cm, 40 g silica gel; 10 X 4 cm, 90 g silica gel; 21 X 4 cm, 120 g silica gel, respectively. These cartridges are available from Biotage, a division of Dyax, 1500 Avon Street Extended, Charlottesville, Virginia, 22902. It is readily appreciated by one of ordinary skill in the art that the purifications and separations performed herein using the above cartridges can also be performed using standard flash chromatography columns prepared in the laboratory using standard flash chromatography silica gel and glass columns; "eq" refers to equivalents; "g" refers to grams; "mg" refers to milligrams; "kPa" refers to kilopascals; "L" refers to liters; "mL" refers to milliliters; "μL" refers to microliters; "mol" refers to moles; "mmol" refers to millimoles; "psi" refers to pounds per square inch; "min" refers to minutes; "h" or "hr" refers to hours; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_f" refers to retention factor; "R_t" refers to retention time; "δ"refers to part per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "HMDS" refers to 1,1,1,3,3,3-hexamethyldisilazane; "DMF" refers to N,N-dimethylformamide; "DMSO" refers to methyl sulfoxide; "LDA" refers to lithium diisopropylamide; "MeOH" refers to methanol; "EtOH" refers to ethanol: "NMP" refers to N-methylpyrrolidone; "t-BuONa" refers to sodium t-butoxide; "BINAP" refers to 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl; "$Pd_2(dba)_3$" refers to tris(dibenzylideneactone)dipalladium (0); "EtOAc" refers to ethyl acetate; "aq" refers to aqueous; "iPrOAc" refers to isopropyl acetate; "Ph" refers to phenyl; "PPh_3" refers to triphenylphosphine; "DEAD" refers to diethyl

azodicarboxylate; "Et_3N" refers to triethylamine; "methyl DAST" refers to dimethylaminosulfur trifluoride; "DAST" refers to diethylaminosulfur trifluoride, "DBU" refers to 1,8-diazabicyclo[5.4.0]undec-7-ene; "TFA" refers to trifluoroacetic acid; "EDCI" refers to 1-ethyl-3-[3-(dimethylamino)propyl]-carbodiimide hydrochloride; "HOBt" refers to hydroxybenztriazole; "*m*-CPBA" refers to m-chloroperoxybenzoic acid; "DME" refers to dimethoxyethane; and "RT" refers to room temperature.

EXAMPLE 1

Preparation of 4-[2-(2,6-Dichlorobenzylthio)ethylamino]-6-methoxyquinazoline.



(i) 6-Methoxyquinazolin-4(3H)-one.

A mixture of 2-amino-5-methoxybenzoic acid (3.34g, 20mmol) and formamide (20mL) was stirred at 130° for 1 hour and then at 160°C for 2 hours. The reaction mixture was then poured into water (300mL). The resulting white flocculent precipitate was collected by filtration, washed with H_2O on the sinter, and dried *in vacuo* at 50°C, to give the product as a fawn solid.

(ii) 4-Chloro-6-methoxyquinazoline

A mixture of 6-methoxyquinazoline-4(3H)-one (3g,17mmol) and phosphorus oxychloride (150mL) was heated under reflux for 20 hours. The reaction mixture was then cooled and evaporated *in vacuo* to give an amber oil. This oil was dissolved in ethyl acetate, and washed sequentially with 2M sodium carbonate, then water, and then saturated sodium chloride solution. The organic phase was then dried over magnesium sulphate, filtered and evaporated *in vacuo* to give the crude product. The crude product was purified by flash chromatography on silica (eluent diethyl ether) to give the product as a white solid.

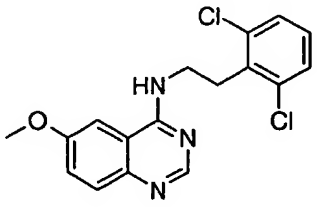
(iii) 4-[2-(2,6-Dichlorobenzylthio)ethylamino]-6-methoxy-quinazoline.

A mixture of 4-chloro-6-methoxyquinazoline (200mg, 1.02mmol), 2-(2,6-dichlorobenzylthio)ethylamine (291mg, 1.23mmol) and diisopropylethylamine (894µl, 5.14mmol) in absolute ethanol (20mL) was stirred at ambient temperature

for 48 hours. The reaction mixture was then evaporated *in vacuo* to give the crude product as an off-white semi-solid/oil. The crude product was purified by flash chromatography on silica (eluent diethyl ether) to give the title compound as a white solid (m.p. 161-3°C).

EXAMPLE 2

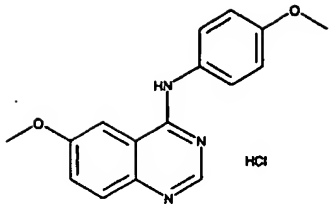
Preparation of 4-[2-(2,6-Dichlorophenyl)ethylamino]-6-methoxyquinazoline.



A mixture of 4-chloro-6-methoxyquinazoline (100mg, 0.51mmol), 2-(2,6-dichlorophenyl)ethylamine (117mg, 0.62mmol) and diisopropylethylamine (447µl, 2.57mmol) in dry dimethylformamide (5mL) was stirred at ambient temperature for 24 hours. The reaction mixture was poured into water (50mL), and extracted with ethyl acetate (3x). The combined organic extracts were washed sequentially with water and saturated sodium chloride solution, then dried over magnesium sulphate, filtered and evaporated *in vacuo* to give the crude product as a light-yellow solid. The crude product was purified by flash chromatography on silica (eluent ethyl acetate) to give the title compound as a white solid. (m.p. 200-201°C).

EXAMPLE 3

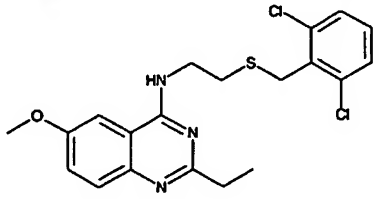
Preparation of 4-(4-Methoxyphenylamino)-6-methoxyquinazoline hydrochloride.



A mixture of 4-chloro-6-methoxyquinazoline (50mg, 0.26mmol), 4-methoxyaniline (158mg, 1.28mmol) and diisopropylethylamine (223µl, 1.28mmol) in dry dimethylformamide (2mL) was stirred at ambient temperature for 60 hours, than at 70°C for 1 hour. The reaction mixture was cooled, poured into water (60mL) and extracted with ethyl acetate (3X). The combined organic extracts were washed sequentially with water and saturated sodium chloride solution, then dried over magnesium sulphate, filtered and evaporated *in vacuo* to give the crude product as a yellow solid. The crude product was purified by flash chromatography on silica (eluent ethyl acetate) to give the free base of the title compound as a white solid. The free base was dissolved in 0.5 molar ethanolic hydrogen chloride and evaporated *in vacuo* to give the title compound as a light-yellow solid (m.p. 262-4°C).

EXAMPLE 4

Preparation of 2-Ethyl-4-[2-(2,6-dichlorobenzylthio)ethylamino]-6-methoxyquinazoline.



(i) 2-Ethyl-6-methoxyquinazolin-4(3H)-one.

An intimate mixture of 2-amino-5-methoxybenzoic acid (2g, 12mmol) and propionamide (12g, 164mmol) was stirred at 150°C for 24 hours. The reaction mixture was allowed to cool, dissolved in the minimum volume of dichloromethane, and

purified by flash chromatography on silica (eluent ethyl acetate) to give the product as a pinkish solid.

(ii) 2-Ethyl-4-chloro-6-methoxyquinazoline.

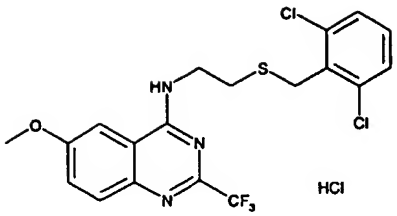
A mixture of 2-ethyl-6-methoxyquinazolin-4(3H)-one (800mg, 3.92mmol) and phosphorus oxychloride (50mL) was heated under reflux for 24 hours. The reaction mixture was allowed to cool and then evaporated *in vacuo*. The residual gum was dissolved in ethyl acetate and washed sequentially with 2M sodium carbonate, water, and then saturated sodium chloride solution. The organic phase was then dried over magnesium sulphate, filtered and the filtrate evaporated *in vacuo* to give the crude product as a brown solid. The crude product was purified by flash chromatography on silica (eluent n-hexane 50% diethyl ether) to give the product as a yellow solid.

(iii) 2-Ethyl-4-[2-(2,6-dichlorobenzylthio)ethylamino]-6-methoxyquinazoline.

A mixture of 2-ethyl-4-chloro-6-methoxyquinazoline (111mg, 0.50mmol), 2-(2,6-dichlorobenzylthioethylamine (142mg, 0.60mmol) and diisopropylethylamine (435µl, 2.5mmol) in dry dimethylformamide (5mL) was stirred at ambient temperature for 24 hours. The reaction mixture was poured into water (100mL) and then extracted with ethyl acetate (3X). The combined organic extracts were washed with water and saturated sodium chloride solution, dried over magnesium sulphate, filtered and evaporated *in vacuo* to give the crude product as a yellow oil. The crude product was purified by flash chromatography on silica (eluent diethyl ether) to give the title compound as a white solid. (m.p. 186-7°C).

EXAMPLE 5

Preparation of 2-Trifluoromethyl-4-[2-(2,6-dichlorobenzylthio)ethylamino-6-methoxyquinazoline hydrochloride.



(i) 2-Trifluoromethyl-6-methoxyquinazolin-4(3H)-one.
An intimate mixture of 2-amino-5-methoxybenzoic acid (3g, 18mmol) and trifluoroacetamide (6.18g, 54mmol) was stirred at 150°C for 5 hours. The reaction mixture was allowed to cool, dissolved in the minimum of dichloromethane and purified by flash chromatography on silica (eluent diethyl ether) to give the product as a pinkish-purple solid.

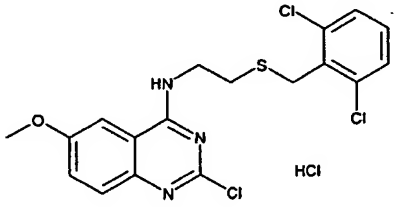
(ii) 2-Trifluoromethyl-4-chloro-6-methoxyquinazoline.
A mixture of 2-trifluoromethyl-6-methoxyquinazoline-4(3H)-one (542mg, 2.22mmol) and phosphorus oxychloride (25mL) was heated under reflux for 24 hours. The reaction mixture was allowed to cool and then evaporated *in vacuo*. The residue was dissolved in ethyl acetate, and washed consecutively with 2M sodium carbonate (2X) and saturated sodium chloride solution. The organic phase was dried over magnesium sulphate, filtered and evaporated *in vacuo* to give the product as a pink solid.

(iii) 2-Trifluoromethyl-4-[2-(2,6-dichlorobenzylthio)-ethylamino-6-methoxyquinazoline hydrochloride.
A mixture of 2-trifluoromethyl-4-chloro-6-methoxyquinazoline (198mg, 0.75mmol), 2-(2,6-dichlorobenzylthio)ethylamine (214mg, 0.91mmol) and diisopropylethylamine (487mg, 3.78mmol) in absolute ethanol (20mL) was stirred at ambient temperature for 20 hours. The reaction mixture was evaporated *in vacuo*, then the residue was redissolved in the minimum of dichloromethane and purified by flash chromatography on silica (eluent hexane 50% diethyl ether) to give the free base of the title compound as a white solid. The free base was dissolved in ethanol, the required

amount of 0.5M ethanolic hydrogen chloride added and the solution evaporated *in vacuo* to give the title compound as a white solid (m.p.139-140°C).

EXAMPLE 6

Preparation of 2-Chloro-4-[2-(2,6-dichlorobenzylthio)ethylamino]-6-methoxyquinazoline hydrochloride.



(i) 2,4-Dihydroxy-6-methoxyquinazoline.

An intimate mixture of 2-amino-5-methoxybenzoic acid (2.5g, 15mmol) and urea (1.52g, 25.4mmol) was stirred at 200°C for 1.5 hours. The reaction mixture was allowed to cool, the solid residue mechanically broken up, and 2M sodium hydroxide (50mL) added. The small amount of insoluble material was removed by filtration, and the filtrate was saturated with carbon dioxide. The resultant greenish precipitate was collected by filtration and dried in vacuo to give the product as a green solid.

(ii) 2,4-Dichloro-6-methoxyquinazoline.

A mixture of 2,4-dihydroxy-6-methoxyquinazoline (1.4g. 7.95mmol) and phosphorus oxychloride (50mL) was heated under reflux for 24 hours. The reaction mixture was cooled, and evaporated *in vacuo*. The residue was dissolved in ethyl acetate, and washed consecutively with 2M sodium carbonate (2x), water and then saturated sodium chloride solution. The ethyl acetate phase was then dried over magnesium sulphate, filtered, and evaporated *in vacuo* to give the crude product as a yellow oil. The crude product was purified by flash

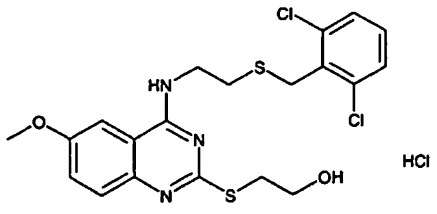
chromatography on silica (eluent diethyl ether 50% hexane) to give the product as a yellow solid.

(iii) 2-Chloro-4-[2-(2,6-dichlorobenzylthio)ethylamino]-6-methoxyquinazoline hydrochloride.

A mixture of 2,4-dichloro-6-methoxy-quinazoline (212mg, 1mmol), 2-(2,6-dichlorobenzylthio)ethylamine (236mg, 1mmol) and diisopropylethylamine (870µl, 5mmol) in dry dimethylformamide (10mL) was stirred at ambient temperature for 48 hours. The reaction mixture was poured into water (50mL), extracted ethyl acetate (3x) and the combined organic extracts washed with water and saturated sodium chloride solution, dried over magnesium sulphate, filtered and evaporated *in vacuo* to give the crude product as a yellow gum. The crude product was purified by flash chromatography on silica (eluent diethyl ether) to give the free base of the title compound as a white solid. The free base was dissolved in 0.5M ethanolic hydrogen chloride (2mL) and evaporated *in vacuo* to give the title compound as a white solid (m.p. 198-200°C).

EXAMPLE 7

Preparation of 2-(2-Hydroxyethylthio)-4-[2-(2,6-dichlorobenzylthio)-ethylamino]-6-methoxyquinazoline hydrochloride.

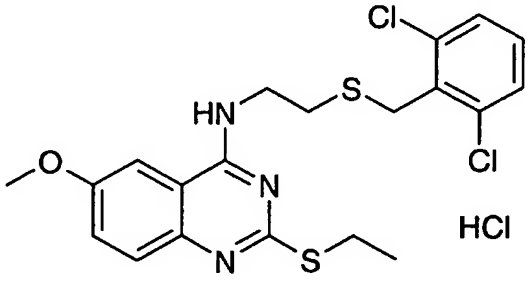


To a mixture of 2-mercaptoethanol (25µl, 0.35mmol) and potassium-tert-butoxide (39mg,0.35mmol) in dry dimethylformamide (2mL) under a nitrogen atmosphere at ambient temperature was added a solution of 2-chloro-4-[2-

(2,6-dichlorobenzylthio)ethylamino]-6-methoxyquinazoline (50mg, 0.12mmol). The reaction mixture was then stirred at 90°C under a nitrogen atmosphere for 1.5 hours. The reaction mixture was then cooled, poured into water (100mL) and extracted with ethyl acetate (3x). The combined organic extracts were washed with water and saturated sodium chloride solution, then dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product as a white gum. The crude product was purified by flash chromatography on silica (eluent diethyl ether) to give the free base of the title compound as a white solid. The free base was dissolved in 0.5M ethanolic hydrogen chloride (2mL) and evaporated *in vacuo* to give the title compound as a white solid (m.p. 222-224°C).

EXAMPLE 8

Preparation of 2-Ethylthio-4-[2-(2,6-dichlorobenzylthio)ethylamino]-6-methoxyquinazoline hydrochloride.

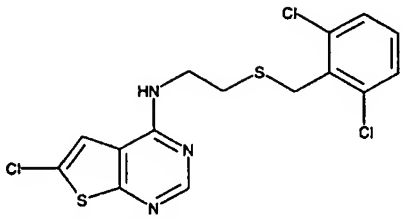


A mixture of 2-chloro-4-[2-(2,6-dichlorobenzylthio)-ethylamino]-6-methoxyquinazoline (100mg, 0.23mmol) and sodium ethylthiolate (27mg, 0.25mmol) in dry dimethylformamide (2mL) was stirred at ambient temperature. After 24 hours a further aliquot of sodium ethylthiolate (27mg, 0.25mmol) was added and stirring at ambient temperature continued for a further 24 hours. The reaction

mixture was diluted with water (50mL) and extracted with ethyl acetate (3x). The combined organic extracts were washed sequentially with water and saturated sodium chloride solution, dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product as a yellow gum. The crude product was purified by flash chromatography on silica (eluent diethyl ether 33% hexane) to give the free base of the title compound as a white solid. The free base was dissolved in 0.5M ethanolic hydrogen chloride and evaporated *in vacuo* to give the title compound as a white solid (m.p. 198-200°C).

EXAMPLE 9

Preparation of 6-Chloro-4-[2-(2,6-dichlorobenzylthio)ethylamino]thieno[2,3-d]pyrimidine hydrochloride.



(i) Methyl-5-chloro-3-cyano-2-thienyliminoformate

A mixture of 2-amino-3-cyano-5-chlorothiophene (500mg, 3.13mmol), trimethylorthoformate (20mL) and cationic ion exchange resin 50wx8-100 (which had been prewashed with methanol and dried in vacuo) was stirred at 80°C for 24 hours. The reaction mixture was then filtered, the filtered solid washed with dichloromethane and methanol, and the combined filtrate and washings evaporated *in vacuo* to give the product as a yellow oil.

(ii) 6-Chloro-3-[2-(2,6-dichlorobenzylthio)ethyl]-thieno[2,3-d]pyrimidin-4(3H)-imine.

A solution of methyl-5-chloro-3-cyano 2-thienyliminoformate (300mg, 1.5mmol) and 2-(2,6-dichlorobenzylthio)ethylamine (407mg. 1.64mmol) in absolute ethanol (12mL) was stirred at ambient temperature for 24 hours. The reaction mixture was evaporated *in vacuo* to give the crude product as a light brown solid.

(iii) 6-Chloro-4-[2-(2,6-dichlorobenzylthio) ethylamino]thieno-[2,3-d]pyrimidine hydrochloride.

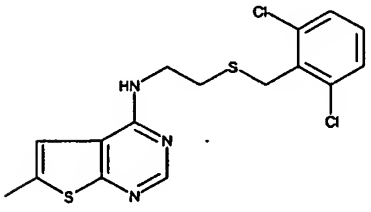
To a solution of 6-chloro-3-[2-(2,6-dichlobenzylthio)-ethyl]thieno[2,3-d]pyrimidin-4(3H)-imine(620mg 1.53mmol) in a 9:1 mixture of dimethylformamide/isopropanol (20mL) was added anionic ion exchange resin 550A-OH (4g), and the suspension was then stirred at 85°C for 48 hours. The reaction mixture was filtered, the filtered solid was washed

with methanol, and the combined filtrate and washings evaporated *in vacuo* to give the crude product as an amber oil. The crude product was purified by flash chromatography on silica (eluent hexane:diethylether = 1:2) to yield the title compound as an off white solid (m.p. 168-70°C).

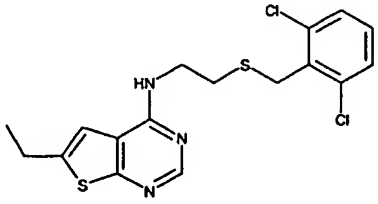
EXAMPLES 10 and 11

Following the method of Example 9, the following compounds were prepared:

EXAMPLE	m.p. (°C)	SALT FORM
10	164-5	Free Base
11	164-5	Free Base



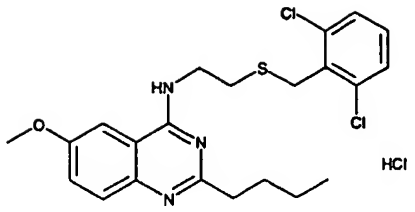
Example 10



Example 11

EXAMPLE 12

Preparation of 2-n-Butyl-4-[2-(2,6-dichlorobenzylthio)ethylamino]-6-methoxyquinazoline.



(i) 2-n-Butyl-6-methoxyquinazolin-4(3H)-one.

An intimate mixture of 2-amino-5-methoxybenzoic acid (2g. 12mmol) and valeramide (16.94g, 167mmol) was stirred at 150°C for 24 hours. The reaction mixture was then cooled, dissolved in dichloromethane (100mL) and purified by flash chromatography on silica (eluent diethyl ether), to give the product as on off-white solid.

(ii) 2-n-Butyl-4-chloro-6-methoxyquinazoline.

A mixture of 2-n-butyl-6-methoxyquinazolin-4(3H)-one (750mg, 3mmol) and phosphorus oxychloride (80mL) was heated under reflux for 24 hours. The reaction mixture was then cooled and evaporated *in vacuo*. The residual gum was dissolved in ethyl acetate and then washed successively with 2M sodium carbonate solution (2x), water and then saturated sodium chloride solution. The organic phase was then dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product as a yellow oil. The crude product was purified by flash chromatography on silica (eluent diethyl ether) to give the product as a yellow oil.

(iii) 2-n-Butyl-4-[2-(2,6-dichlorobenzylthio)ethylamino]-6-methoxyquinazoline.

A solution of 2-n-butyl-4-chloro-6-methoxyquinazoline (125mg, 0.5mmol), 2-(2,6-dichlorobenzylthio)ethylamine (114mg, 0.6mmol) and diisopropylethylamine (434µl, 2.5mmol) in dry dimethylformamide (5mL) was stirred at ambient temperature for 24 hours. The reaction mixture was poured into water (50mL) and extracted with ethyl acetate (3x). The combined organic extracts were washed with water and saturated sodium chloride solution, dried over magnesium

sulfate, filtered and evaporated *in vacuo* to give the crude product as a yellow gum. The crude product was purified by flash chromatography on silica (eluent diethyl ether) to give the free base of the product as a white glass. The free base was dissolved in absolute ethanol (10mL) and a 0.5M ethanolic hydrogen chloride solution (528µl) was added. The solution was then cooled at 5°C for 16 hours and the crystalline precipitate collected by filtration and dried in vacuo, to yield the title compound as white crystals. (m.p. 202-3°C).

EXAMPLES 13 TO 25

The compounds of Examples 13 to 25 were prepared following the method of Example 12. The amine starting material used in the preparation of the compound of Example 21 was prepared as follows:

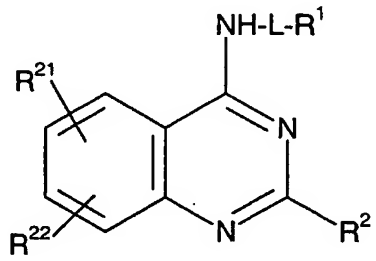
(i) 2-(2,6-dichlorobenzylsulphoxidyl)ethylamine

To a solution of 2-(2,6-dichlorobenzylthio)ethylamine (2.36g, 10mmol) in methanol (200mL) was added, with ice-bath cooling, a solution of sodium periodate (2.57g, 12mmol) in water (200mL). The reaction mixture was then filtered, and the methanol evaporated in vacuo. The remaining aqueous phase was then saturated with sodium chloride and extracted with ethyl acetate (3X). The combined organic extracts were washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the product as a yellow oil, which slowly crystallized on standing.

(ii) 2- (2,6-dichlorobenzylsuphonyl)ethylamine.

To a solution of 2-(2,6-dichlorobenzylsulphoxidyl)ethylamine (504mg, 2mmol) in methanol (8mL) was added a solution of potassium peroxymonosulfate (1.23g, 2mmol) in water (60mL) and the mixture stirred at ambient temperature for 24 hours.

The reaction mixture was then evaporated *in vacuo* to dryness, re-suspended in saturated sodium chloride solution and neutralized with saturated sodium bicarbonate solution. The aqueous phase was then extracted with ethyl acetate (3X) and the combined organic extracts dried over magnesium sulfate, filtered and evaporated in vacuo to give the product as a white gum.



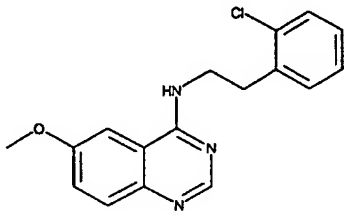
R^{21} R^{22}	R^2	L-R^1	Ex	m.p. (°C)	SALT FORM
6-Methyl	H	2-(2,6-Dichlorobenzyl-thio)ethyl	13	175-6	FB
6-Methyl	H	Bicyclo[2.2.1]hept-2-yl	14	>240	FB
6-Methyl	H	(1R,2R,3R,5S)-2,6,6-trimethylbicyclo-[3.1.1]hept-2-yl	15	214-16	FB
6-Methoxy	methyl	2-(2,6-Dichlorobenzylthio)ethyl	16	213-15	HCl
6-Methoxy	n-Propyl	2-(2,6-Dichlorobenzylthio)ethyl	17	145-7	FB
6-Methoxy	n-propyl	2-(2-Chlorophenethyl)	18	151-4	FB
6-Methoxy	Iso-propyl	2-(2,6-dichlorobenzylthio)ethyl	19	201-3	HCl
6-Methoxy	Iso-butyl	2-(2,6-Dichlorobenzyl-thio)ethyl	20	152-4	FB
6-Methoxy	H	2-(2,6-Dichlorobenzyl-sulphonyl)ethyl	21	214-16	FB
7-Chloro	H	2-(2,6-Dichlorobenzyl-thio)ethyl	22	178-80	FB
7-Chloro	H	(1R,2R,3R,5S)-2,6,6-trimethylbicyclo-[3.1.1]hept-2-yl	23	198-99	FB
6,8-Dichloro	H	2-(2,6-Dichlorobenzyl-thio)ethyl	24	152-4	FB
6,8-Dichloro	H	(1R,2R,3R,5S)-2,6,6-Trimethylbicyclo-[3.1.1]hept-2-yl	25	250-2	FB

FB = Free base

HCl = hydrochloride salt

EXAMPLE 26

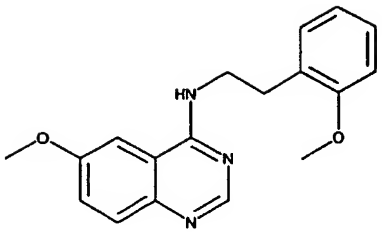
Preparation of 4-[2-(2-chlorophenyl)ethylamino]-6-methoxyquinazoline



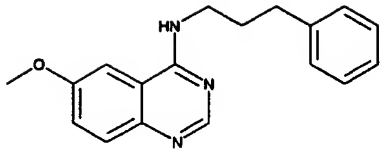
A mixture of 4-chloro-6-methoxyquinazoline (4.86mg, 0.025mmol), 2-(2-chlorophenylethylamine (11.6mg, 0.075mmol) and poly(4-vinylpyridine) (50mg) in dry dimethylformamide (1mL) was stirred at ambient temperature for 24 hours, then at 50°C for 2 hours. The reaction mixture was cooled, then polybenzaldehyde resin [1.7mmol/g] (147mg) and more dimethylformamide (1mL) were added. The mixture was then stirred at ambient temperature for a further 20 hours. The reaction mixture was filtered, and the filtered solid washed with dimethylformamide (2 x 1mL). The filtrate was diluted with methanol (2mL) and subjected to ion-exchange chromatography [500mg/3mL SCX column which had been pre-washed with methanol (2.5mL)] The column was washed with methanol (2.5mL) and then the product was eluted with 2.3M methanolic ammonia (2.5mL). The eluent was evaporated under nitrogen at 70°C to yield the title compound as a white solid. (MS: m/e 314, 316)

EXAMPLES 27-29

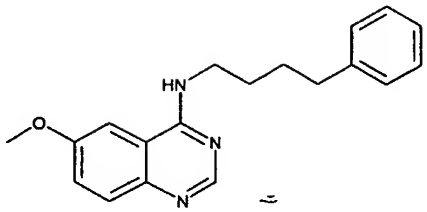
The following compounds were prepared following the method of Example 26.



Example 27



Example 28



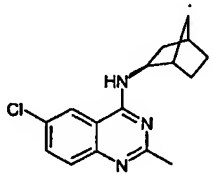
Example 29

L-R^1	EXAMPLE	M. S. (m/e)	SALT FORM
2-(2-Methoxy-phenyl)ethyl	27	310	FB
3-Phenylpropyl	28	294	FB
4-Phenylbutyl	29	308	FB

FB = Free base

EXAMPLE 30

Preparation of 4-(Bicyclo[2.2.1]hept-2-ylamino)-6-chloro-2-methylquinazoline.



(i) 2-(Acetylamino)-5-chlorobenzoic acid.

To a solution of 5-chloro-2-aminobenzoic acid (5.15g, 30mmol) in dry pyridine (100mL) was added, dropwise, with ice-bath cooling, acetyl chloride (2.2mL, 30mmol). The mixture was then allowed to warm to ambient temperature and stirred for 24 hours. The reaction mixture was evaporated to dryness *in vacuo*, water added, and extracted with ethyl acetate (3X). The combined organic extracts were washed with 1M hydrochloric acid (2x), water and then saturated sodium chloride solution. The organic phase was then dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the product as a white solid.

(ii) 6-Chloro-2-methyl-4H-3,1-benzoxazin-4-one.

To a suspension of 2-(acetylamino)-5-chlorobenzoic acid (5.8g, 27.2mmol) in dry diethyl ether (100mL) was added, dropwise, triethylamine (4.2mL, 29.9mmol). To the resultant clear solution was added, dropwise, ethyl chloroformate (2.9mL, 29.9mmol), and the mixture then stirred at ambient temperature for 24 hours. The reaction mixture was filtered, and the filtrates evaporated *in vacuo* to give the product as an off white solid.

(iii) 6-Chloro-2-methylquinazoline-4(3H)-one.

A mixture of 6-chloro-2-methyl-4H-3,1-benzoxazin-4-one (2.8g, 14.3 mmol) and 0.880 ammonia solution (20mL) was heated in a sealed tube at 100°C for 2 hours.

The reaction mixture was cooled and evaporated in vacuo to give the product as an off white solid.

(iv) 4,6-Dichloro-2-methylquinazoline.

A mixture of 6-chloro-2-methylquinazolin-4-(3H)-one (2.60g, 13.4mmol) and phosphorus oxychloride (125mL) was heated under reflux for 2 hours. The reaction mixture was then cooled, and then evaporated *in vacuo* to give an amber gum, which was dissolved in ethyl acetate and washed with (1) 2M

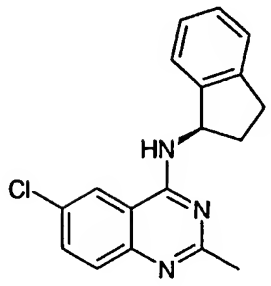
sodium carbonate solution (2x), water and then saturated sodium chloride solution. The organic phase was then dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product as an orange solid. The crude product was purified by flash chromatography on silica (eluent diethyl ether) to give the product as a yellow solid.

(v) 4-(Bicyclo[2.2.1]hept-2-ylamino)-6-chloro-2-methylquinazoline.

A solution of 4,6-dichloro-2-methylquinazoline (106mg, 0.5mmol) and exo-2-aminonorbornane (61mg, 0.55mmol) in absolute ethanol (6mL) was stirred at ambient temperature for 20 hours. The reaction mixture was evaporated *in vacuo* to give the crude product as a yellow oil. The crude product was purified by flash chromatography on silica (eluent : hexane 50% diethyl ether) to give the title compound as an off-white solid (m.p. 156°C).

EXAMPLE 31

The compound of Example 31 was prepared by the method of Example 30.

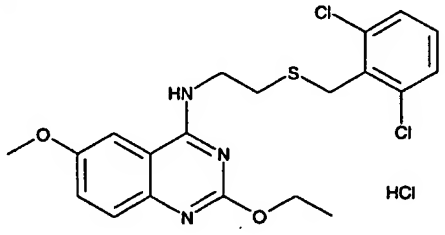


L-R^1	EXAMPLE	M.P.(°C)	SALT FORM
2,3-Dihydro-1H-inden-1-yl	24	200	FB

FB = Free Base

EXAMPLE 32

Preparation of 4-[2-(2,6-dichlorobenzylthio)ethylamino]2-ethoxy-6-methoxyquinazoline hydrochloride



(i) 2,4-Dihydroxy-6-methoxyquinazoline

An intimate mixture of 2-amino-5-methoxy benzoic acid (2g, 12mmol) and urea (1.22g, 20.3mmol) was stirred at 200°C for 1.5 hours. The reaction mixture was then cooled, the solid residue partially broken up mechanically, and then partially dissolved in 2M sodium hydroxide solution (10mL) at ambient temperature. The fine suspension was filtered, and the

filtrate was saturated with carbon dioxide ("dry-ice" pellets), and cooled at 5°C for 20 hours. The precipitate was collected by filtration and dried *in vacuo* at 50°C to give the product as a green solid.

(ii) 2,4-Dichloro-6-methoxyquinazoline

A mixture of 2,4-dihydroxy-6-methoxyqunazoline (1.4g, 7.9mmol) and phosphorus oxychloride (50mL) was heated under reflux for 24 hours. The reaction mixture was cooled and evaporated *in vacuo*. The residue was dissolved in ethyl acetate, and washed with 2M sodium carbonate solution (2x), water and then saturated sodium chloride solution. The organic phase was then dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product as a yellow oil. The crude product was purified by flash chromatography on silica (eluent diethyl ether) to give the product as a yellow solid.

(iii) 2-Chloro-4-[2-(2,6-dichlorobenzylthio)ethylamino]-6-methoxyquinazoline.

A solution of 2,4-dichloro-6-methoxyquinazoline (212mg, 1mmol), 2-(2,6-dichlorobenzyethio)ethylamine (236mg, 1mmol) and diisopropylethylamine (870µl, 5mmol) in dry dimethylformamide (10mL) was stirred at ambient temperature for 48 hours. The reaction mixture was poured into water (100mL) and extracted with ethyl acetate (3x). The combined organic extracts were washed with water and saturated sodium chloride, dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product as a yellow semi crystalline oil. The crude product was purified by flash chromatography on silica (eluent diethyl ether) to give the product as a white solid.

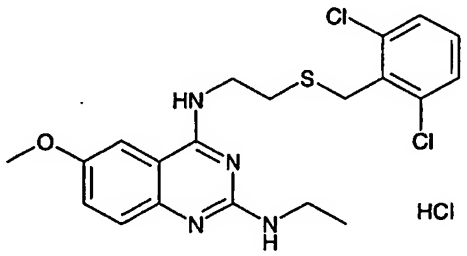
(iv) 4-[2-(2,6-Dichlorobenzylthio)ethylamino]-2-ethoxy-6-methoxyquinazoline hydrochloride.

A mixture of 2-chloro-4-[2-(2,6-dichlorobenzylthio)-ethylamino]-6-methoxyquinazoline (60mg, 0.14mmol) and 5%

sodium ethoxide solution (5mL) was heated at 100°C for 20 hours. The reaction mixture was cooled and poured into water (70mL). The aqueous phase was extracted with ethyl acetate (3x) and the combined organic extracts were washed with water and saturated sodium chloride solution, dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product as an amber gum. The crude product was purified by flash chromatography on silica (eluent diethyl ether) to give the free base of the product as a yellow foam. The free base was dissolved in 0.5M ethanolic hydrogen chloride (2mL) and then evaporated *in vacuo* to yield the title compound as a yellow solid (m.p. 227-8°C).

EXAMPLE 33

The compound of Example 33 was prepared by the method of Example 32, except that, in step (iv), ethylamine (30% w/w solution in ethanol) and Hunigs base were used in place of sodium ethoxide.



R^2	EXAMPLE	M.P. (°C)	SALT FORM
NH Ethyl	26	217-18	HCl

HCl = hydrochloride salt

EXAMPLES 34 TO 41

(i) 4-Amino-3-cyano-1,2,5,6-tetrahydropyridine

A cooled (-65°C) mechanically stirred solution of 3,3'-iminodipropionitrile (41.0g, 300mmol, weight corrected for purity of 90%) under nitrogen was treated dropwise with 1.0 N lithium bis(trimethylsilyl)amide/tetrahydrofuran (330 mL, 330 mmol) at a rate to keep the pot temperature below -50°C (a precipitate soon began to form). The solution was stirred at -60°C for 1h after the addition was complete, then warmed to -20°C over 30 min and quenched with 5N aqueous ammonium chloride (75 mL, 375 mmol). Water (100 mL) and 2-propanol (100 mL) were added, and the mixture was separated into two layers. The aqueous layer was extracted with 3:1 ethyl acetate/2-propanol containing a little methanol (6x150 mL, alternatively, continuous extraction can be used), and the combined organic extracts and initial organic layer were dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The residual solid was triturated from acetonitrile/2-propanol (two crops) to afford 4-amino-3-cyano-1,2,5,6-tetrahydropyridine (25.9g, 70%) as a white solid; mp 160 - 162°C.

(ii) 4-Amino-3-cyano-1-(1,1-Dimethylethoxycarbonyl)-1,2,5,6-tetrahydropyridine

A suspension of 4-amino-3-cyano-1,2,5,6-tetrahydro-pyridine (3.70g, 30 mmol) in anhydrous tetrahydrofuran (40 mL) was treated with di-t-butyl dicarbonate (7.64g, 35 mmol), after which bubbling ensued. After 2h at ambient temperature, some mild heating was applied to drive the reaction to completion, then the solution was concentrated *in vacuo*. The residue was taken up in methylene chloride and loaded onto silica gel, then eluted initially with methylene chloride, then with 4:1 ethyl acetate/methylene chloride to collect product. This yielded the subject compound (5.89g, 88%) as a white solid.

(iii) 4-((2-(2-Chlorophenyl)ethyl)amino)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine

A solution of 4-amino-3-cyano-1-(1,1-dimethylethoxy-carbonyl)-1,2,5,6-tetrahydropyridine (2.90g, 13 mmol) in trimethyl orthoformate (40 mL) was treated with two drops of methanesulfonic acid and heated to 60-65°C under nitrogen for 45 min, then another two drops of acid was added and heating continued for 45 additional minutes. The solution was concentrated *in vacuo* to a yellow solid, and this was taken up in absolute ethanol (40 mL), treated with 2-(2-chlorophenyl)ethylamine (2.57g, 16.5 mmol), and stirred at ambient temperature for 18h. The solution was concentrated *in vacuo*, redissolved in 9:1 ethanol/water (40 mL), placed in a 125 mL pressure bottle, heated to 100°C for 18h, then concentrated *in vacuo*. The residue was chromatographed on silica gel (eluted with 7:3 ethyl acetate/methylene chloride, then ethyl acetate) to afford 4.16g (82%) of the Boc-amine. A portion of this obtained from several batches (5.84g, 15 mmol) was dissolved in 1:1 methylene chloride/trifluoroacetic acid (40 mL), and bubbling ensued. The mixture was stirred for 2h, then concentrated *in vacuo*. Some toluene was added, and concentration was continued to eliminate excess trifluoroacetic acid, then the salt was triturated from ether and taken up in tetrahydrofuran (100 mL). DOWEX^{R} 550A OH hydroxide resin (25g) was added, and the mixture was stirred for a few minutes and filtered. The filtrate was concentrated *in vacuo*, and the residue was triturated from ether to afford the subject compound (4.21g, 97%) as a pale yellow solid. Mass calculated For $C_{15}H_{17}ClN_4$: 288.8; M+1 found 289.2

Following a similar procedure, the following compounds were also prepared:

4-((2-(2,6-dichlorobenzylthio)ethyl)amino-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine and 4-(2,3-dihydro-1H-inden-2-yl)amino-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine.

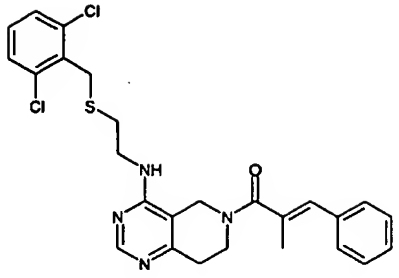
(iv) Final products

Commercially available acid chlorides, sulphonyl chlorides, isocyanates, and isothiocyanates [100 µL, 0.8 M in anhydrous tetrahydrofuran, 80 µmol per well], the appropriate product of step (III) [100µL, 0.6 M in anhydrous tetrahydrofuran, 60 µmol per well], and 300 µL tetrahydrofuran were agitated overnight (18h) in a modified plate containing 2 mL glass wells (96) on an orbital shaker (plates placed on sides for better mixing), after Dowex-OH 550-A anion resin (60 mg) had been added to wells containing acid chlorides and sulphonyl chlorides to absorb any HCl formed.

The contents were filtered through a filter plate by uptake and delivery from an 8-way Eppendorf Repeater pipette fitted with 1 mL disposable tips. Scavenging strategy as shown for electrophiles involved mixed bed polyamine resin and isocyanate resin (~60mg, ~2meq/g each) in one pot with THF added as necessary for proper solvation. The plates were shaken on an orbital shaker overnight (18h). TLC's taken in 1:19 MeOH:CH_2Cl_2 showed pure products, as did mass spec. Compounds were salted with HCl (~900 µmol/well / 2umol/µL = 450 µL/well 2 M HCl), and concentrated to remove excess HCl.

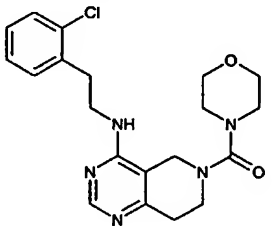
EXAMPLE 34

Preparation of 4-((2-(2,6-dichlorobenzylthio)ethyl)amino)-6-(2-methyl-3-phenyl)prop-2-enoyl)-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine: mass calculated: 512.3; M+1 found 513.7.



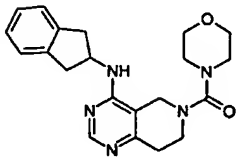
EXAMPLE 35

Preparation of 4-((2-(2-chlorophenyl)ethyl)amino)-6-morpholinocarbonyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine: mass calculated: 401.3; M+1 found 402.8.



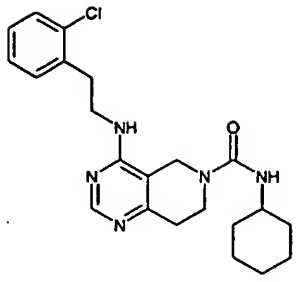
EXAMPLE 36

Preparation of 4-(2,3-dihydro-*1H*-inden-2-yl)amino-6-morpholinocarbonyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine: mass calculated: 379.5; M+1 found 380.5.



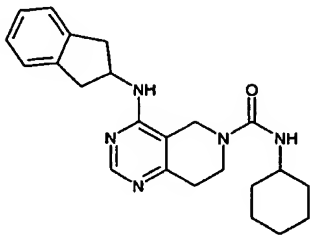
EXAMPLE 37

Preparation of 4-((2-(2-chlorophenyl)ethyl)amino)-6-cyclohexylamino-carbonyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine: mass calculated: 413.4; M+1 found 414.8.



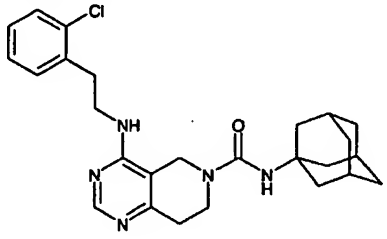
EXAMPLE 38

Preparation of 4-(2,3-dihydro-*1H*-inden-2-yl)amino-6-cyclohexylamino-carbonyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine: mass calculated: 391.5; M+1 found 392.5.



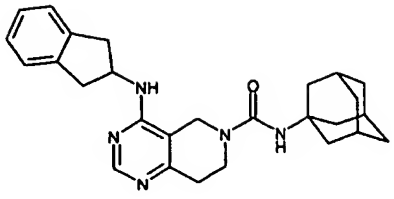
EXAMPLE 39

Preparation of 4-((2-(2-chlorophenyl)ethyl)amino)-6-adamantanylamino-carbonyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine: mass calculated: 465.4; M+1 found 466.7.



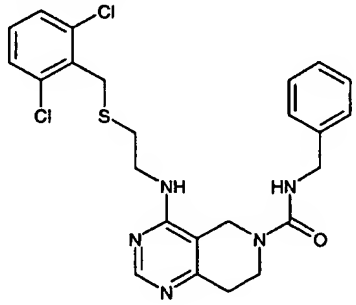
EXAMPLE 40

Preparation of 4-(2,3-dihydro-*1H*-inden-2-yl)amino-6-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine: mass calculated: 443.6; M+1 found 444.7.



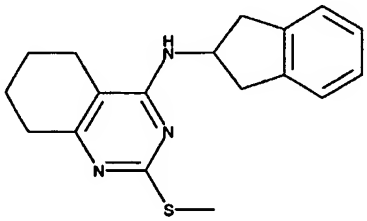
EXAMPLE 41

Preparation of 4-((2-(2,6-dichlorobenzylthio)ethyl)amino)-6-benzylaminocarbonyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine: mass calculated: 501.2; M+1 found 502.5.



EXAMPLE 42

Preparation of N-(2,3-dihydro-*1H*-inden-2-yl)-2-(methylthio)-5,6,7,8-tetrahydroquinazolin-4-amine

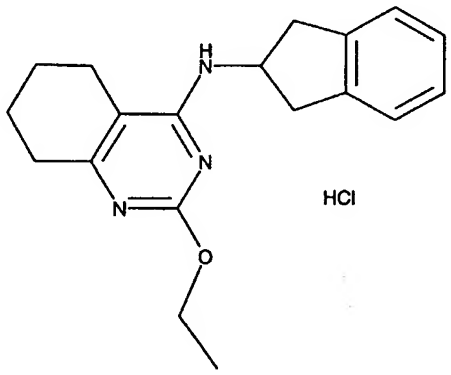


2-Methylthio-4-chloro-4,5,6,7-tetrahydroquinazoline (Chem. Pharm. Bull. **31** (1983) 2254)(3.36g, 15.6 mmol) and 2-aminoindane (2.1g, 15.8 mmol) were dissolved in N-methylpyrrolidinone (20mL), potassium carbonate (2.4g, 17.4 mmol) was added, the mixture was stirred under N_2 and heated at 100°C for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced

pressure. The resulting dark oil was purified by column chromatography on silica gel (eluent chloroform/methanol) to give 5.5g of a solid which was recrystallized from ethyl acetate/hexane (59:1) to give the title compound as a white solid of melting point 185-187°C.

EXAMPLE 43

Preparation of N-(2,3-dihydro-*1H*-inden-2-yl)-2-(ethoxy)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.



(i) N-(2,3-dihydro-*1H*-inden-2-yl)-2-(methylsulfonyl)-5,6,7,8-tetrahydroquinazolin-4-amine.

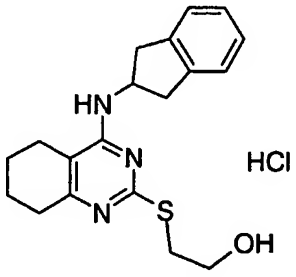
N-(2,3-dihydro-*1H*-inden-2-yl)-2-(methylthio)-5,6,7,8-tetrahydroquinazolin-4-amine (5g, 16.1 mmol) was dissolved in acetone/water (19:1)(100mL) and stirred at ambient temperature. Oxone (20.5g, 33.3 mmol) dissolved in water (25mL) was added portionwise to the stirred reaction mixture. When addition was complete the mixture was left to stir at ambient temperature for 18 hours. The mixture was concentrated under reduced pressure and partitioned between ethyl acetate and water. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent chloroform/methanol, 59:1) to give 5.2g of the title compound as a white solid of melting point 145-147°C.

(ii) N-(2,3-dihydro-*1H*-inden-2-yl)-2-(ethoxy)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride

Sodium (400mg, 17.4 mmol) was dissolved in ethanol (50mL) at ambient temperature under nitrogen. N-(2,3-dihydro-*1H*-inden-2-yl)-2-(methylsulfonyl)-5,6,7,8-tetrahydroquinazolin-4-amine (600mg, 17.4 mmol) was added and the mixture was heated for 3 hours at 50°C. The mixture was concentrated under reduced pressure and partitioned between ethyl acetate and water. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:3) to give a yellow oil (300mg) which was taken up in ethanol (5mL), 0.5N ethanolic HCl (2mL) was added followed by diethyl ether (40mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 137-140°C.

EXAMPLE 44

N-(2,3-dihydro-*1H*-inden-2-yl)-2-(2-hydroxyethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.

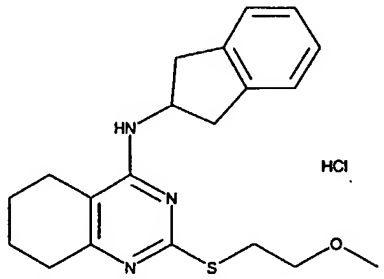


The product of Example 43(i) (500mg, 1.45 mmol) was dissolved in N-methylpyrrolidinone (7mL) and stirred at ambient temperature under nitrogen. Potassium-*tert*-butoxide (500mg, 4.4 mmol) was added followed by 2-mercaptoethanol

(1mL). The mixture was stirred and heated under nitrogen at 85°C for 4 hours. The reaction mixture was poured into aqueous ammonium chloride solution (150mL) and extracted into ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane 1:1) to give a colorless oil which was taken up in ethanol (5mL). 0.5N ethanolic HCl (2mL) was then added followed by diethyl ether (40mL). A white solid crystallized on standing and was collected by filtration to give the title compound, 230mg, melting point 173-176°C.

EXAMPLE 45

Preparation of N-(2,3-dihydro-*1H*-inden-2-yl)-2-(2-methoxyethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.

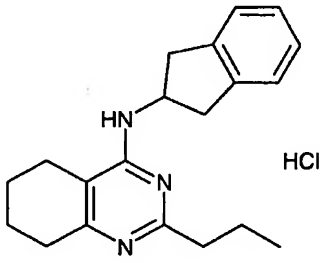


The product of Example 43(i) (1.2g, 3.36 mmol) was dissolved in N-methylpyrrolidinone (15mL) and stirred at ambient temperature under nitrogen. Potassium-*tert*-butoxide (560mg, 5 mmol) was added followed by 2-methoxyethanethiol (500mg, 5.4mmol). The mixture was stirred and heated under nitrogen at 95°C for 48 hours. The reaction mixture was poured into aqueous ammonium chloride solution (150mL) and extracted into ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:2) to give a

yellow oil which was taken up in ethanol (5mL). 0.5N Ethanolic HCl (4mL) was then added followed by diethyl ether (70mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 181-183°C.

Example 46

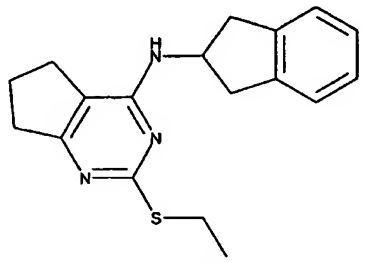
Preparation of N-(2,3-dihydro-*1H*-inden-2-yl)-2-propyl-5,6,7,8-tetrahydroquinazolin-4-amine.



4-Chloro-5,6,7,8-tetrahydro-2-propylquinazoline (690mg, 3.18mmol)(GB Patent 1,152,883, CA 71 112965) and 2-aminoindane (450mg, 3.38 mmol) were dissolved in N-methylpyrrolidinone (10mL). Potassium carbonate (465mg, 3.36 mmol) was added, the mixture was stirred under N_2 and heated at 100°C for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:3) to give the title compound, as a white solid of melting point 193-195°C.

EXAMPLE 47

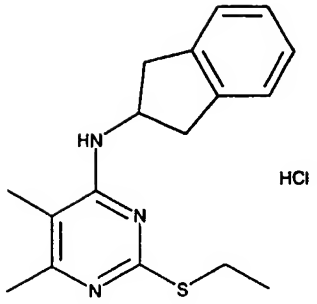
Preparation of N-(2,3-dihydro-*1H*-inden-2-yl)-2-(ethylthio)-6,7-dihydro-*5H*-cyclopenta[*d*]pyrimidin-4-amine.



2-Ethyl-1,5,6,7-tetrahydro-*4H*-cyclopentapyrimidin-4-one (700mg, 3.6mmol)(Nucleosides Nucleotides (1994) 891) was suspended under nitrogen in phosphorus oxychloride/1,2-dichloroethane (1:1)(10mL) and heated under reflux for 15 hours. The reaction mixture was concentrated under reduced pressure and taken up in chloroform. The crude product was washed with cold dilute sodium hydrogen carbonate solution, dried (magnesium sulfate), filtered and concentrated under reduced pressure to give a dark oil. The oil was taken up in N-methylpyrrolidinone (10mL), potassium carbonate (465mg, 3.36 mmol) and 2-aminoindane (475mg, 3.6mmol) were added, and the reaction mixture was heated under nitrogen at 90°C for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:3) to give the title compound, as a white solid which was recrystallized from ethyl acetate/hexane, melting point 154-156°C.

EXAMPLE 48

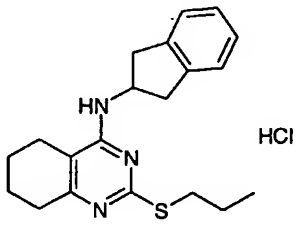
Preparation of N-(2,3-dihydro-*1H*-inden-2-yl)-2-(ethylthio)-5,6-dimethylpyrimidine-4-amine hydrochloride.



Prepared in a similar manner to Example 47 above from 2-aminoindane and 4-chloro-2-(ethylthio)-5,6-dimethylpyrimidine (C.A. 91 123704). Melting point 104-106°C.

EXAMPLE 49

Preparation of N-(2,3-dihydro-*1H*-inden-2-yl)-2-(propylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.

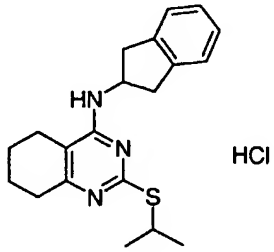


N-(2,3-dihydro-*1H*-inden-2-yl)-2-(methylsulfonyl)-5,6,7,8-tetrahydroquinazolin-4-amine (600mg, 1.75 mmol) was dissolved in N-methylpyrrolidinone (15mL) and stirred at ambient temperature under nitrogen. Potassium-*tert*-butoxide (560mg, 5 mmol) was added followed by 1-propanethiol (550mg, 7.25mmol). The mixture was stirred and heated under nitrogen at 90°C for 18 hours. The reaction mixture was poured into aqueous ammonium chloride solution (150mL) and extracted into ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:3) to give a yellow oil which was taken up in ethanol (5mL), 0.5N

ethanolic HCl (4mL) was added followed by diethyl ether (70mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 185-187°C.

EXAMPLE 50

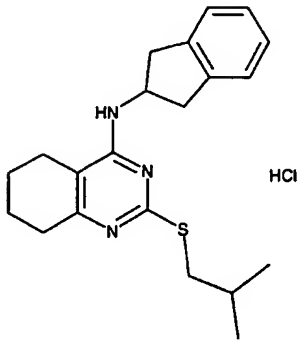
Preparation of N-(2,3-dihydro-*1H*-inden-2-yl)-2-(1-methylethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.



Prepared in a similar manner to Example 49 above from N-(2,3-dihydro-*1H*-inden-2-yl)-2-(methylsulfonyl)-5,6,7,8-tetrahydroquinazolin-4-amine and 2-propanethiol. Melting point 177-179°C.

EXAMPLE 51

Preparation of N-(2,3-dihydro-*1H*-inden-2-yl)-2-(2-methylpropylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.

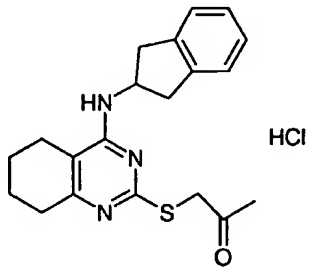


Prepared in a similar manner to Example 49 above from N-(2,3-dihydro-*1H*-inden-2-yl)-2-(methylsulfonyl)-5,6,7,8-

tetrahydroquinazolin-4-amine and 2-methylpropane-1-thiol. Melting point 180-182°C.

EXAMPLE 52

Preparation of N-(2,3-dihydro-*1H*-inden-2-yl)-2-(2-oxo-propylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.

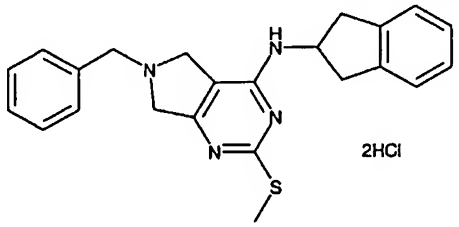


N-(2,3-dihydro-*1H*-inden-2-yl)-2-(methylsulfonyl)-5,6,7,8-tetrahydroquinazolin-4-amine (660mg, 1.85 mmol) was dissolved in N-methylpyrrolidinone (15mL) and stirred at ambient temperature under nitrogen. Potassium-*tert*-butoxide (265mg, 2.36 mmol) was added followed by 1-mercapto-2-propanol (230mg, 2.5mmol). The mixture was stirred and heated under nitrogen at 90°C for 18 hours. The reaction mixture was poured into aqueous ammonium chloride solution (150mL) and extracted into ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane) to give N-(2,3-dihydro-1H-inden-2-yl)-2-(2-hydroxpropylthio)-5,6,7,8-tetrahydroquinazolin-4-amine as a yellow oil (700mg) which showed a main peak of 356 by mass spectroscopy. This oil was oxidized under Swern conditions (Tet. (1978) 34, 1651). The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane) to give a clear oil (350mg) which was taken up in ethanol (5mL), 0.5N ethanolic HCl (4mL) was added followed by diethyl ether (70mL). A white solid crystallized

on standing and was collected by filtration to give the title compound, melting point 177-180°C.

EXAMPLE 53

Preparation of 6-Benzyl-N-(2,3-dihydro-1*H*-indenyl)-2-(methylthio)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-4-amine.



(i) 6-Benzyl-2-(methylthio)-3,5,6,7-tetrahydro-4*H*-pyrrolo[3,4-*d*]pyrimidin-4-one.

Sodium carbonate (6g, 56mmol) was dissolved in water (200mL) and stirred at ambient temperature, S-Methylisothiouronium sulfate (10g, 36mmol) was added and the mixture was stirred until all the solids were dissolved. Ethyl-1-benzyl-4-oxopyrrolidine-3-carboxylate (8.8g 35.6mmol)(Synth. Comm. (1996) 1659) was added and the mixture was stirred at ambient temperature for 22 hours. Chloroform (200mL) was added, the organic was collected, dried (magnesium sulfate), filtered and concentrated under reduced pressure to afford an off-white solid. Column chromatography (eluent chloroform/methanol) gave the title compound, 3.9g as a white solid. Mass spectroscopy showed 274 (MH^+) as the major peak.

(ii) 6-Benzyl-4-chloro-2-(methylthio)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine.

6-Benzyl-2-(methylthio)-3,5,6,7-tetrahydro-4*H*-pyrrolo[3,4-*d*]pyrimidin-4-one (2.3g 8.4mmol) was dissolved in 1,2-dichloroethane (15mL) at ambient temperature under nitrogen, phosphorus oxychloride (20mL) was added and the mixture was heated under reflux under nitrogen overnight. The reaction

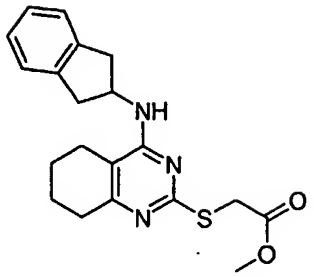
mixture was concentrated under reduced pressure, taken up in chloroform and washed with cold dilute aqueous sodium hydrogen carbonate solution. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure to a dark oil. Column chromatography (eluent chloroform/methanol) gave the title compound, 2.05g as a dark oil. Mass spectroscopy showed 293/295 (MH^+) as the major peak.

(iii) 6-Benzyl-N-(2,3-dihydro-1*H*-indenyl)-2-(methylthio)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidin-4-amine.

6-Benzyl-4-chloro-2-(methylthio)-6,7-dihydro-5*H*-pyrrolo[3,4-*d*]pyrimidine (0.8g, 2.75mmol) and 2-aminoindane (350mg, 2.63 mmol) were dissolved in N-methylpyrrolidinone (10mL), potassium carbonate (0.5g, 3.6 mmol) was added, the mixture was stirred under N_2 and heated at 90°C for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane) to give 200mg of a clear oil which was taken up in ethanol (5mL). 0.5N ethanolic HCl (3mL) was added followed by diethyl ether (70mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 152.5-154°C.

EXAMPLE 54

Preparation of Methyl 2-((4-(2,3-dihydro-1*H*-inden-2-ylamino)-5,6,7,8-tetrahydroquinazolin-2-yl)thio)acetate.



A 4mL Reacti-Vial was charged sequentially with a 0.24M solution of potassium *tert*-butoxide in dry N-methyl pyrrolidinone (0.5mL), a 0.24M solution of methyl thioglycolate in dry N-methyl pyrrolidinone (0.5mL) and a 0.06M solution of N-(2,3-dihydro-1H-inden-2-yl)-2-(methylsulfonyl)-5,6,7,8-tetrahydroquinazolin-4-amine in dry N-methyl pyrrolidinone (0.5mL). The Vial was flushed with nitrogen and capped. The contents of the Vial were heated to 80°C and stirred for 64 hours. The Vial was cooled and its contents quenched with saturated aqueous ammonium chloride solution (1mL). Chloroform (1mL) was added, and the Vial was recapped and agitated vigorously to extract the organic material into the chloroform phase. A 3mL cartridge containing an octadecyl C18 disc was charged with the contents of the Vial. Only the organic phase passed through the disc and this recovered solution was treated with methanol (1mL). The mixture was then passed through a 3mL cartridge containing 500mg of methanol-conditioned benzenesulfonic acid resin under gravity. The column was washed with fresh methanol (3mL). The initial filtrate and washings were discarded. Finally, the column was eluted with 2N ammonia in methanol (3mL) to release the purified product from the resin. Solvent was removed from the eluate *in vacuo* to yield 2.9mg of methyl 2-{[4-(2,3-dihydro-1*H*-inden-2-ylamino)-5,6,7,8-tetrahydroquinazolin-2-yl]-thio}acetate (26%) as a dark brown oil.

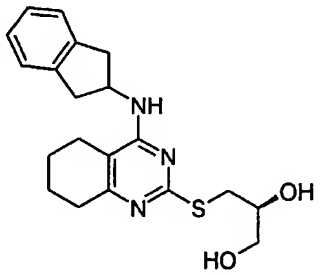
m/z 370 $[M+H]^+$. ^1H n.m.r. data: 7.22ppm (s, 4H); 4.99-4.95ppm (m, 1H); 3.91ppm (s, 2H); 3.70ppm (s, 3H); 3.35ppm (d, 2H); 2.90ppm (d, 2H), 2.19ppm (bs 2H), 1.79ppm (bs, 6H).

EXAMPLES 55-64

Following a method similar to that described in Example 54, the following compounds were prepared:

EXAMPLE 55

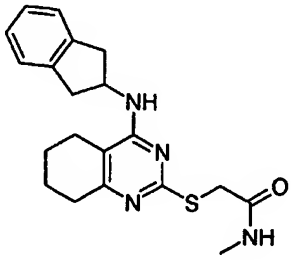
Preparation of 3-((4-(2,3-dihydro-1*H*-inden-2-ylamino)-5,6,7,8-tetrahydroquinazolin-2-yl)thio)propane-1,2-diol.



m/z 372 $[M+H]^+$. ^1H n.m.r. data: 7.20-7.18ppm (m, 4H); 5.00-4.93ppm (m, 2H); 4.01-3.95ppm (m, 1H); 3.73-3.66ppm (m, 2H); 3.49-3.31ppm (m, 2H); 3.29ppm (d, 2H); 2.85ppm (dd, 2H); 2.67ppm (bs, 2H); 2.18ppm (bs, 2H); 1.78ppm (bs, 4H).

EXAMPLE 56

Preparation of 2-((4-(2,3-dihydro-1*H*-inden-2-ylamino)-5,6,7,8-tetrahydroquinazolin-2-yl)thio)-*N*-methylacetamide.

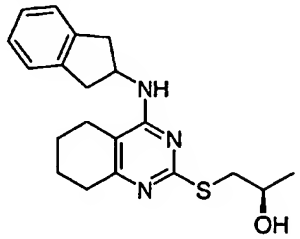


m/z 369 $[M+H]^+$. ^1H n.m.r. data: 7.35ppm (bs, 1H); 7.22-7.17ppm (m, 4H); 5.00-4.89ppm (m, 2H); 3.82ppm (s, 2H);

3.46-3.35ppm (m, 2H); 2.95-2.83ppm (m, 2H); 2.81ppm (s, 3H); 2.71ppm (bs, 2H); 2.17ppm (bs, 2H); 1.79ppm (bs, 4H).

EXAMPLE 57

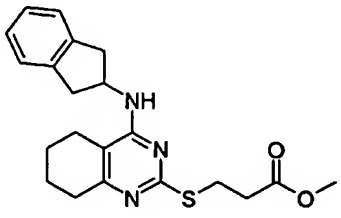
Preparation of 1-((4-(2,3-dihydro-1*H*-inden-2-ylamino)-5,6,7,8-tetrahydroquinazolin-2-yl)thio)propan-2-ol.



m/z 356 $[M+H]^+$. ^1H n.m.r. data: 7.22-7.17ppm (m, 4H); 4.97-4.93ppm (m, 2H); 4.22-4.16ppm (m, 1H); 3.47-3.31ppm (m, 3H); 3.20-3.13ppm (m, 1H); 2.91ppm (dd, 2H); 2.74ppm (bs, 2H); 2.18ppm (bs, 2H); 1.78ppm (bs, 4H); 1.30ppm (d, 3H).

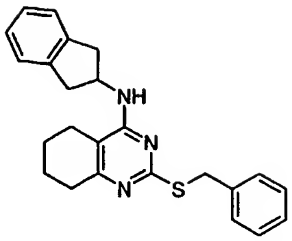
EXAMPLE 58

Preparation of Methyl 3-((4-(2,3-dihydro-1*H*-inden-2-ylamino)-5,6,7,8-tetrahydroquinazolin-2-yl)thio)propanoate
m/z 384 $[M+H]^+$.



EXAMPLE 59

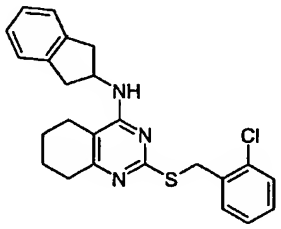
Preparation of 2-(benzylthio)-*N*-(2,3-dihydro-1*H*-inden-2-yl)-5,6,7,8-tetrahydroquinazolin-4-amine.
m/z 388 $[M+H]^+$.



EXAMPLE 60

Preparation of 2-((2-chlorobenzyl)thio)-*N*-(2,3-dihydro-1*H*-inden-2-yl)-5,6,7,8-tetrahydroquinazolin-4-amine

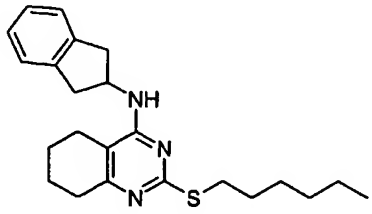
m/z 422 $[M+H]^+$.



EXAMPLE 61

Preparation of N-(2,3-dihydro-1*H*-inden-2-yl)-2-(hexylthio)-5,6,7,8-tetrahydroquinazolin-4-amine.

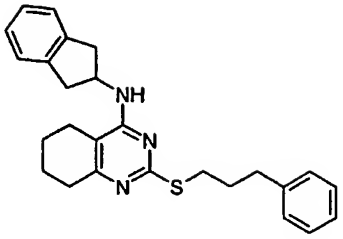
m/z 382 $[M+H]^+$.



EXAMPLE 62

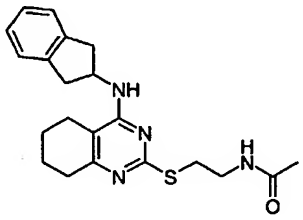
Preparation of N-(2,3-dihydro-1*H*-inden-2-yl)-2-((3-phenylpropyl)thio)-5,6,7,8-tetrahydroquinazolin-4-amine

m/z 416 $[M+H]^+$.



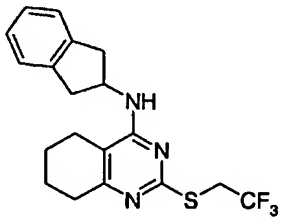
EXAMPLE 63

Preparation of *N*-(2-((4-(2,3-dihydro-1*H*-inden-2-ylamino)-5,6,7,8-tetrahydroquinazolin-2-yl)thio)ethyl)acetamide m/z 383 $[M+H]^+$.



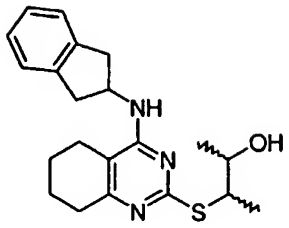
EXAMPLE 64

Preparation of *N*-(2,3-dihydro-1*H*-inden-2-yl)-2-((2,2,2-trifluoroethyl)-thio)-5,6,7,8-tetrahydroquinazolin-4-amine m/z 380 $[M+H]^+$.



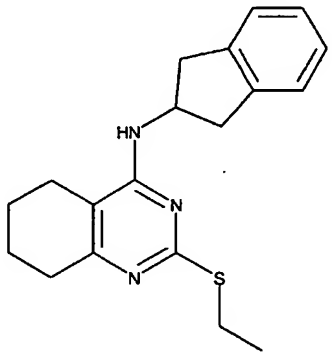
EXAMPLE 65

Preparation of 3-((4-(2,3-dihydro-1*H*-inden-2-ylamino)-5,6,7,8-tetrahydroquinazolin-2-yl)thio)butan-2-ol m/z 370 $[M+H]^+$.



EXAMPLE 66

Preparation of N-(2,3-dihydro-1H-inden-2-yl)-2-ethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine.



(i) 2-(ethylthio)-5,6,7,8-tetrahydroquinazolin-4(3H)-one

Methyl cyclohexanon-2-carboxylate (1.0g, 6.4mmol) was added dropwise at ambient temperature to a stirred solution of aqueous sodium carbonate (1.35g, 1.28mmol) in water (30mL) and S-ethylthiouronium hydrobromide (1.77g, 9.6mmol). The mixture was stirred at ambient temperature for 3 hours under N_2. A white precipitate was observed, and collected by filtration, washed with ether, then dried *in vacuo* at 40°C, to give a white solid.

(ii) 4-chloro-2-(ethylthio)-5,6,7,8-tetrahydro quinazoline

A mixture of 2-(ethylthio)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (700mg, 3.3mmol) and phosphorous oxychloride (20mL) were heated to reflux for 48 hours. The reaction mixture was allowed to cool down to ambient temperature and

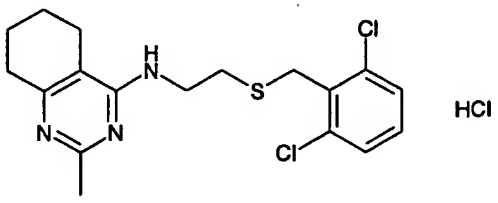
evaporated *in vacuo*. The residue was taken up in ethyl acetate and washed with aqueous sodium hydrogen carbonate (2 x 50mL). The organic phase was dried with magnesium sulfate, filtered and evaporated *in vacuo* to give a yellow oil which crystallized on standing.

(iii) N-(2,3-dihydro-1H-inden-2-yl)-2-ethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine.

A mixture of 4-chloro-2-(ethylthio)-5,6,7,8-tetrahydroquinazoline (940mg, 3.26 mmol), 2-aminoindane (477mg, 3.58mmol), potassium carbonate (451mg, 3.26 mmol) and 1-methyl-2-pyrrolidinone (20mL) were heated at 90°C under N_2 for 20 hours. The reaction mixture was allowed to cool down to ambient temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed several times with brine. The organic phase was dried with magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product. The crude product was purified by flash chromatography on silica (eluent: 60% hexane, 40% ethyl acetate) to give the title compound as a cream solid. M/Z 326 $[M+H]^+$.

EXAMPLE 67

Preparation of N-(2-((2,6-dichlorobenzyl)thio)ethyl)-2-methyl-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.



(i) 2-methyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one

Sodium metal (190mg) was dissolved in ethanol (20mL). Once the sodium had reacted, the mixture was *in vacuo* and the

residue was added to a stirred mixture of methyl cyclohexanon-2-carboxylate (2.0g, 1.28 mmol) and acetamidine hydrochloride (1.46g, 1.53 mmol) at ambient temperature. This reaction mixture was heated to reflux for 48 hours. The reaction mixture was cooled to ambient temperature, poured into water (30mL) and extracted with ethyl acetate (2 x 20 mL). The organic phase was dried with magnesium sulfate, filtered and evaporated *in vacuo* to give a yellow oil, 1.78g.

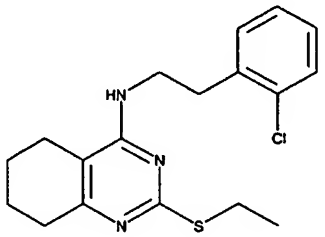
(ii) 4-chloro-2-methyl-5,6,7,8-tetrahydroquinazoline
A mixture of 2-methyl-5,6,7,8-tetrahydroquinazolin-4(3H)-one (1.75g, 1.07 mmol), phosphorous oxychloride (50mL) and 1,2-dichloroethane (20mL) were heated to reflux for 48 hours. The reaction mixture was allowed to cool down and evaporated *in vacuo*. The residue was taken up in ethyl acetate and washed with aqueous sodium hydrogen carbonate, carefully, (2x50 mL). The organic phase was dried with magnesium sulfate, filtered and evaporated *in vacuo* to give a clear oil, 1.4g.

(iii) N-(2-((2,6-dichlorobenzyl)thio)ethyl)-2-methyl-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.
A mixture of 4-chloro-2-methyl-5,6,7,8-tetrahydroquinazoline (200mg, 1.09 mmol), 2-(2,6-dichlorobenzylthio)ethylamine (283mg, 1.19 mmol) and 1-methyl-2-pyrrolidinone (20mL) was heated at 90°C under N_2 for 48 hours. The reaction mixture was allowed to cool to ambient temperature. The reaction mixture was poured into water and extracted with ethyl acetate (2 x 20mL). The organic phase was washed with water then brine. The organic phase was dried with magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product. The crude product was purified by flash chromatography on silica (eluent: 5% methanol: 95% ethyl

acetate). The free base was dissolved in ethanol and then was added dropwise 0.5M ethanolic hydrogen chloride. The mixture was then evaporated *in vacuo* to give the title compound as a white solid, (m.p. 249-250°C).

EXAMPLE 68

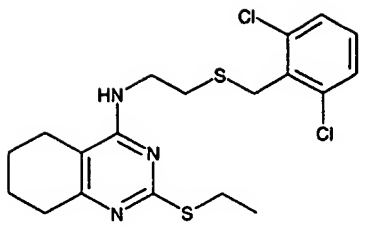
Preparation of N-(2-(2-chlorophenyl)ethyl)-2-(ethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine.



(i) A mixture of 4-chloro-2-(ethylthio)-5,6,7,8-tetrahydroquinazoline (200mg, 0.877mmol), 2-(2-chlorophenyl)ethylamine (150mg, 0.965mmol) and 1-methyl-2-pyrrolidinone (20mL) were heated at 90°C under N_2 for 48 hours. The reaction mixture was allowed to cool to ambient temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with water then brine, dried with magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product. The crude product was purified by flash chromatography on silica (eluent 80% hexane / 20% ethyl acetate) to give the title compound as a white solid, (m.p. 132-133.5°C).

EXAMPLE 69

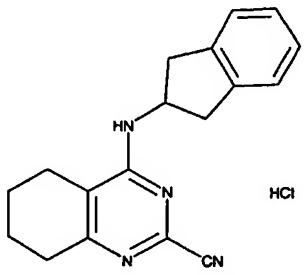
Preparation of N-(2-((2,6-dichlorobenzyl)thio)ethyl)-2-(ethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine.



A mixture of 4-chloro-2-(ethylthio)-5,6,7,8-tetrahydroquinazoline (200mg, 0.877mmol), 2-(2-dichloro benzylthio)ethylamine (228mg, 0.965 mmol) and N-methylpyrrolidinone (20mL) were heated to 90°C under N_2 for 48 hours. The reaction mixture was allowed to cool to ambient temperature. The reaction mixture was then poured into water and extracted with ethyl acetate. The organic phase was washed with water then brine, then dried with magnesium sulfate, filtered and evaporated *in vacuo* to give a crude product. The crude product was purified by flash chromatography on silica (eluent 80% hexane / 20% ethyl acetate) to give the title compound, as a cream solid (m.p. 127-129°C).

EXAMPLE 70

Preparation of 4-(2,3-dihydro-1H-inden-2-yl methyl)-5,6,7,8-tetrahydroquinazoline-2-carbonitrile hydrochloride.

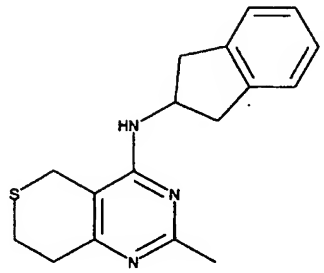


N-(2,3-dihydro-1H-inden-2-yl)-2-(methylsulfonyl)-5,6,7,8-tetrahydroquinazolin-4-amine (560mg, 1.63mmol) and potassium cyanide (560mg, 8.61mmol) in dry dimethylformamide, (8mL) were heated to 100°C for 96 hours under N_2. The reaction mixture was allowed to cool to

ambient temperature, diluted with ethyl acetate, washed with water then brine. The organic phase was dried with magnesium sulfate, filtered and evaporated *in vacuo* to give a crude product. The crude product was purified by flash chromatography on silica (eluent 40% hexane / ethyl acetate). The free base was dissolved in ethanol (5mL), treated with 0.5N ethanolic HCl (2mL), and evaporated *in vacuo*. Diethyl ether was slowly added (1mL). A tan solid crystallized on standing and was collected by filtration to afford the title compound, (m.p. 181.5 - 183°C).

EXAMPLE 71

Preparation of N-(2,3-dihydro-1H-inden-2-yl)-2-methyl-7,8-dihydro-5H-thieno[4,3-d]pyrimidin-4-amine.



(i) Methyl 4-oxotetrahydro-2H-thiopyran-3-carboxylate

Dimethyl 3,3'-thiodipropionate (5.0g, 24.0mmol) was dissolved in diethyl ether (60mL). Sodium methoxide (3.6mg, 52.8 mmol) was added to the reaction mixture. The resulting slurry was stirred for 6 hours under reflux. The reaction mixture was allowed to cool to ambient temperature. Acetic acid (5mL) followed by water (25mL) was added to the reaction mixture. The ether layer was extracted and washed with brine (x2). The organic phase was dried with magnesium sulfate, filtered and evaporated *in vacuo* to obtain a crude oil. The crude oil was purified by flash chromatography on silica (eluent 80% hexane/ethyl acetate) to obtain a colorless oil, 1.28g.

(ii) 2-methyl-3,5-7,8-tetrahydro-4H-thiino [4,3-d] pyrimidin-4-one.

Sodium metal (190mg) was dissolved in ethanol (20mL). Once the sodium had reacted the mixture was evaporated *in vacuo* and the residue was added to a stirred mixture of methyl 4-oxotetrahydro-2H-thiopyran-3-carboxylate (1.39g, 7.98mmol) and acetamidine hydrochloride (905mg, 9.57mmol) at ambient temperature. This reaction mixture was then heated to reflux for 48 hours. The reaction mixture was allowed to cool to ambient temperature, poured into water and extracted with ethyl acetate (2 x 30mL). The organic phase was dried with magnesium sulfate, filtered and evaporated *in vacuo* to give a colorless oil, 979mg.

(iii) 4-chloro-2-methyl-3,5,7,8-tetrahydro-4H-thiino[4,3-d]pyrimidine

A mixture of 2-methyl-3,5-7,8-tetrahydro-4H-thiino (4,3-d)pyrimidin-4-one(979mg, 5.38mmol) and phosphorous oxychloride (40mL) were heated to reflux for 48 hours. The reaction mixture was allowed to cool down to ambient temperature and evaporated *in vacuo*. The residue was taken up in ethyl acetate and washed carefully with aqueous sodium hydrogen carbonate. The organic phase was dried with magnesium sulfate, filtered and evaporated *in vacuo* to give a yellow oil, 410mg.

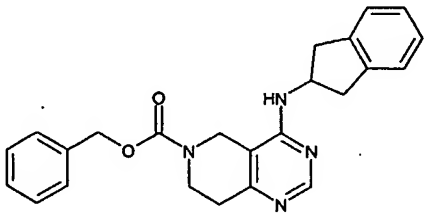
(iv) N-(2,3-dihydro-1H-inden-2-yl)-2-methyl-7,8-dihydro-5H-thiino[4,3-d]pyrimidin-4-amine.

4-chloro-2-methyl-3,5,7,8-tetrahydro-4H-thiino[4,3-d]-pyrimidine (380mg, 1.9mmol) and 2-aminoindane (303mg, 2.28mmol), Hunigs base (1.22g, 9.5mmol) and dimethylformamide (30mL) were stirred for 96 hours at ambient temperature. This mixture was diluted with ethyl

acetate and washed with water then brine. The organic phase was dried with magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product. The crude product was purified by prep HPLC at 254 nm, (3464.KR100-5C18) (95A/5W/0.2NH_3). The title compound was obtained as a light tan solid,(m.p. 147-149°C).

EXAMPLE 72

Preparation of Benzyl 4-(2,3-dihydro-1H-inden-2-ylamino)7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate.



(i) 4-amino-1,2,5,6-tetrahydropyridine-3-carbonitrile. A stirred solution of 3,3-iminodipropionitrile (2.0g, 1.62mmol) in dry tetrahydrofuran (20mL) at -70°C via a cardice acetone bath under nitrogen was treated with 2N lithium diisopropylamine (8.9mL, 1.78mmol) over twenty minutes, keeping the temperature below -50°C. After the addition the solution was stirred for 1 hour at -60°C. The mixture was warmed to -20°C over 30 minutes and quenched with 5N ammonium chloride (10mL), water (5mL) and isopropyl alcohol (5mL). The aqueous layer was extracted with 3:1 ethyl acetate / isopropyl alcohol containing a little methanol. The combined organic extracts and initial layer were dried with magnesium sulphate, filtered and evaporated *in vacuo*. The residue solid was triturated from acetonitrile/isopropyl alcohol. A cream solid was obtained, 721mg.

(ii) Benzyl 4-amino-5-cyano-3,6-dihydropyridine-1(2H)-

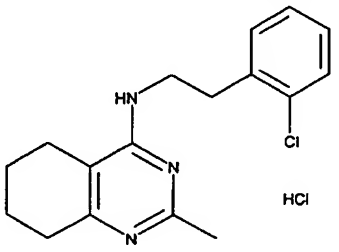
carboxylate.
4-amino-1,2,5,6-tetrahydropyridine-3-carbonitrile (1.0g, 8.13mmol) was dissolved in acetone (60mL) and aqueous potassium carbonate (6.74g, 48.8mmol) and cooled to 0°C. The mixture was then treated with benzyl chloroformate (4.64mL, 32.5mmol). The mixture was allowed to warm up to ambient temperature, and was stirred for 24 hours. The mixture was then filtered and the filtrate was evaporated *in vacuo*. The residue was acidified with potassium hydrogen sulfate and extracted with chloroform. It was then dried with magnesium sulfate, filtered and evaporated *in vacuo* to obtain the crude product. The crude product was purified by flash chromatography on silica (eluent 60% ethyl acetate/40%hexane) to give a pale yellow oil, 1.37g.

(iii) Benzyl 4-(2,3-dihydro-1H-inden-2-ylamino)7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate.
A mixture of benzyl 4-amino-5-cyano-3,6-dihydro pyridine-1(-2H)-carboxylate (1.37g, 5.83mmol) and biorad A950w-X8 sulfonic acid resin (2.5g) after being washed with methanol and dried in anhydrous trimethyl orthoformate (37mL), were stirred at 85°C for 24 hours, under nitrogen. The mixture was filtered and the filter cake was rinsed with dichloromethane then methanol. The filtrate was concentrated *in vacuo*. The residue was then taken up in ethanol (30mL) and treated with 2-aminoindane (1.05g, 7.87mmol). This mixture was stirred at ambient temperature for 48 hours. The solution was evaporated *in vacuo*, the residue was taken up in 9:1 DMF/IPA (40mL) and treated with Dowex® 550A-OH hydroxide resin (9.3g) then heated to 90°C under nitrogen for 48 hours. The mixture was allowed to cool and filtered the filter cake was rinsed with methanol. The filtrate was evaporated *in vacuo* to obtain a brown oil. The crude product was purified by flash chromatography on

silica (eluent 100% ethyl acetate) to give the title compound as a brown solid. M/Z 267 $[M+H]^+$.

EXAMPLE 73

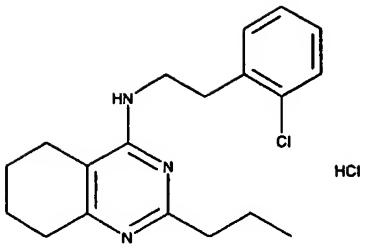
Preparation of N-(2-(2-chlorophenyl)ethyl)-2-methyl-5,6,7,8-tetrahydroquinazolin-4-amine, hydrochloride.



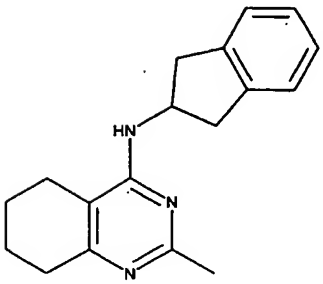
A mixture of 4-chloro-2-methyl-5,6,7,8-tetra-hydroquinazoline (250mg, 1.37mmol), 2-(2-chloro phenyl)ethylamine (234mg, 1.5mmol), potassium carbonate (189mg, 1.37mmol) and methyl-2-pyrrolidinone (20mL) was heated to 90°C under N_2 for 24 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed several times with water. The organic phase was dried with magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product. The crude product was purified by flash chromatography on silica (eluent 100% ethyl acetate) to give a yellow oil, which was taken up in ethanol (5mL). 0.5N Ethanolic HC1 (2 mL) was added, followed by diethyl ether (30 mL). A white solid crystallized on standing and was collected by filtration to give the title compound, m.p. 227-228.5°C.

EXAMPLES 74 AND 75

The compounds of Examples 74 and 75 were prepared following a method similar to that described in Example 73.



Example 74

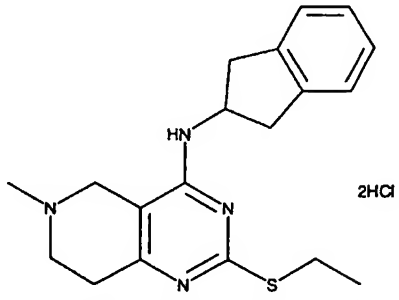


Example 75

X^1-L-R^1	R^2	m.p°C	Salt form	Example
2-(2-chloro phenylethyl) -amino	Propyl	199-201	HCl	74
2,3-dihydro-1H-inden-2-ylamino	Methyl	138-129	FB	75

EXAMPLE 76

N-(2,3-dihydro-1H-inden-2-yl)-2-(ethylthio)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4-amine dihydrochloride



(i) Ethyl 1-methyl-4-oxopiperidine-3-carboxylate.

Ethyl 4-[(3-ethoxy-3-oxopropyl)(methyl)amino]butanoate (Orgsyn Vol III 1955, P258)(3.0g, 1.29mmol) in dichloromethane (20mL) was added dropwise over 10 minutes to a cooled solution of 1N titanium (IV) chloride (12.98mL,

1.29mmol) at -15°C in dichloromethane (20mL) under nitrogen. This temperature was maintained for 1 hour. The reaction mixture was then treated with triethylamine (3.9mL, 2.38mmol). The mixture was maintained at -15°C for 4 hours then left to warm up to ambient temperature. This mixture was left stirring for 24 hours. The reaction mixture was poured into 10% sodium chloride solution (30mL) and adjusted to pH 8-9 using 2N sodium hydroxide. A precipitate formed, and this was filtered and the filter cake was washed with dichloromethane. The organic phase was separated and dried with magnesium sulfate, filtered and evaporated *in vacuo* to afford the product, 1.43g.

(ii) 2-(ethylthio)-6-methyl-5,6,7,8-tetrahydro pyrido[4,3-d]pyrimidin-4(3H)-one.
Ethyl 1-methyl-4-oxopiperidine-3-carboxylate (1.43g, 8.31mmol), sodium carbonate (1.76g, 16.6mmol) and 5-ethylthiourea hydrobromide (2.3g, 12.4mmol) in distilled water (40mL) were stirred under nitrogen at ambient temperature for 24 hours. The mixture was saturated with sodium chloride and extracted with dichloromethane. The organic phase was dried with magnesium sulfate, filtered and evaporated in vacuo, to obtain 1.73g of a yellow oil.

(iii) 4-chloro-2-(ethylthio)-6-methyl-3,4,5,6,7,8-hexahydropyrido[4,3-d]pyrimidine.
A mixture of 2-(ethylthio)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidin-4(3H)-one (1.73g, 8.12mmol) and phosphorous oxychloride (70mL) and 1,2-dichloroethane (25mL) were heated to reflux for 48 hours. The reaction mixture was allowed to cool to ambient temperature and evaporated *in vacuo*. The residue was taken up in ethyl acetate and washed with aqueous sodium hydrogen carbonate. The organic phase was dried with magnesium sulfate, filtered

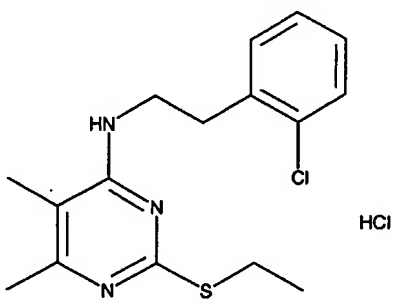
and evaporated *in vacuo* to give 1.12g of a brown/green solid.

(iv) N-(2,3-dihydro-1H-inden-2-yl)-2-(ethylthio)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]-pyrimidin-4-amine dihydrochloride.

A mixture of 4-chloro-2-(ethylthio)-6-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (300mg, 1.23mmol), 2-aminoindane (180mg, 1.35mmol), potassium carbonate (169mg, 1.23mmol) and 1-methyl-2-pyrrolidinone (20mL) were heated at 90°C under nitrogen for 24 hours. The reaction mixture was allowed to cool at ambient temperature. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed several times with brine. The organic phase was dried with magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product. The crude product was purified by flash chromatography on silica (eluent 20% ethyl acetate / 80% methanol) to give a yellow oil. This was taken up in ethanol (5mL), and 0.5N ethanolic HCl (2mL) was added followed by diethyl ether (30mL). A yellow solid crystallized on standing and was collected by filtration to give the title compound m.p. 253-256°C.

EXAMPLE 77

Preparation of N-(2-(2-chlorophenyl)ethyl)-2-(ethylthio)-5,6-dimethyl pyrimidin-4-amine, hydrochloride.



A mixture of 6-chloro-2-(ethylthio)-4,5-dimethyl-1,6-dihydropyrimidine (200mg, 0.098mmol) and 2-(2-chlorophenyl)ethylamine (168mg, 1.08mmol) was reacted as described in Example 76 to produce the title compound. The crude reaction product was purified by flash chromatography on silica (eluent 60% ethyl acetate / 40% hexane). The title compound was obtained. m.p. 154-156°C.

EXAMPLE 78

Preparation of N-(2,3-dihydro-1*H*-inden-2-yl)-4-(ethylthio)-3,5-diazatricyclo[6.2.1.$0^{2,7}$]undeca-2,4,6-trien-6-amine, hydrochloride.

(i) 4-(Ethylthio)-2-hydroxy-3,5-diazatricyclo[6.2.1.$0^{2,7}$]-undec-3-en-6-one.

Sodium carbonate (4.3g, 40mmol) was dissolved in water (150mL) and stirred at room temperature, S-ethylisothiouronium bromide (3.7g, 20mmol) was added and the mixture was stirred until all the solids were dissolved. 3-Methoxycarbonylnorbornan-2-one (3g 17.85mmol)(Heterocycles 38(1994) 2715) was added and the mixture was stirred at room temperature for 22 hours. Chloroform (100mL) was added, the organic was collected, dried (magnesium sulphate), filtered and concentrated under reduced pressure to an off-white solid. Column chromatography (eluent chloroform/methanol 19:1) gave the title compound as a white solid. Mass spectroscopy showed 241 (MH^+) as the major peak.

(ii) 6-Chloro-4-(ethylthio)-3,5-diazatricyclo[6.2.1.$0^{2,7}$]-undeca-2,4,6-triene.

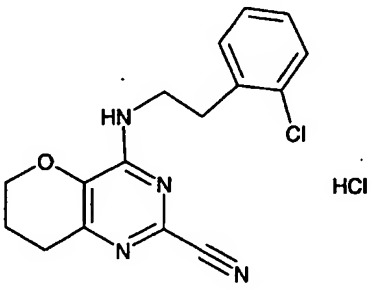
4-(Ethylthio)-2-hydroxy-3,5-diazatricyclo[6.2.1.$0^{2,7}$]-undec-3-en-6-one (450mg, 1.875mmol) was dissolved in 1,2-dichloroethane (5mL) at room temperature under nitrogen. Phosphorus oxychloride (5mL) was added and the mixture was heated under reflux under nitrogen overnight. The reaction

mixture was concentrated under reduced pressure, taken up in chloroform and washed with cold dilute aqueous sodium hydrogen carbonate solution. The organic phase was dried (magnesium sulphate), filtered and concentrated under reduced pressure to give the title compound as a dark oil. Mass spectroscopy showed 241 and 243 (MH^+) as the major peaks.

(iii) 6-Chloro-4-(ethylthio)-3,5-diazatricyclo-[6.2.1.$0^{2,7}$]undeca-2,4,6-triene (445mg, 1.85mmol) and 2-aminoindane (350mg, 2.63 mmol) were dissolved in N-methylpyrrolidinone (10mL), potassium carbonate (0.3g, 2.17 mmol) was added, the mixture was stirred under N_2 and heated at 90°C for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulphate), filtered and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane 1:4) to give a white solid which was taken up in ethanol (3mL), 0.5N ethanolic HCl (3mL) was added followed by diethyl ether (70mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 183-185°C.

Example 79

Preparation of 4-[2-(2-Chloro-phenyl)-ethylamino]-7,8-dihydro-6H-pyrano[3,2-d]pyrimidine-2-carbonitrile, hydrochloride.



(i) 4-Chloro-2-methylsulfanyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidine

To a solution of sodium carbonate (powder, 2.39 g, 22.5 mmol) in ethanol (12.0 mL) was added *S*-methyl(isothiourea) sulfate (2.72 g, 9.75 mmol). The mixture was stirred at room temperature for 15 min, while a solution of ethyl 3-oxotetrahydropyran-2-carboxylate (7.50 mmol) in ethanol (3.0 mL) was added in a dropwise fashion. The mixture was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo. Water and dichloromethane were added. The pH was adjusted to 6 by addition of acetic acid. The aqueous layer was extracted with dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was mixed with phosphorus oxychloride (4.0 mL). The mixture was heated to reflux for 2h. The mixture was cooled to room temperature and concentrated in vacuo to remove the excess of reagent. After dilution with dichloromethane, the resulted dark solution was added dropwise slowly with stirring into a cold mixture of saturated sodium bicarbonate solution with some ice. The mixture was then extracted with dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Silica gel, elution with 5% ether in dichloromethane) to afford the intermediate title compound as a light brown solid. (124 mg, 0.574 mmol, 12% for 2 steps). m/z 216.9 [M+1].

(ii) 4-Chloro-2-methylsulfonyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidine

To a solution 4-chloro-2-methylsulfanyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidine (124 mg, 0.574 mmol) in dichloromethane (5.74 mL) was added sodium bicarbonate (241

mg, 2.87 mmol) and *m*-chloroperoxybenzoic acid (354 mg, 57-80%). The mixture was stirred at room temperature for 2 hours, then diluted with water and extracted with dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Silica gel, elution with 50% EtOAc in hexane) to afford the intermediate title compound as a light brown solid. (111 mg, 0.448 mmol, 78%). m/z 248.9 [M+1].

(iii) [2-(2-Chloro-phenyl)-ethyl]-(2-methanesulfonyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidin-4-yl)-amine

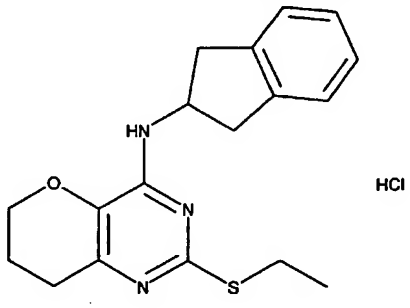
To a solution of 4-chloro-2-methylsulfonyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidine (55.8 mg, 0.225 mmol) in anhydrous NMP (1.25 mL) was added 2-(2-chlorophenyl)ethylamine (42.0 mg, 0.270 mmol). To this solution was added diisopropylethylamine (58.2 mg, 0.078 mL, 0.450 mmol) dropwise slowly and at room temperature. The mixture was then heated at 50 degree for 16h. Water (50 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, gradient elution with 20% ether in CH2C12) then afforded the intermediate title compound (83 mg, 0.225 mmol, 100%) as a brown solid. m/z 368.0 [M+1].

(iv) To a solution of the above [2-(2-chloro-phenyl)-ethyl]-(2-methanesulfonyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidin-4-yl)-amine (83 mg, 0.225 mmol) in NMP (1.0 mL) and DMSO (0.5 mL) was added tetrabutylammonium cyanide (121 mg, 0.450 mmol) and KCN (147 mg, 2.25 mmol). The mixture was heated to 120 degree for 72 hours. The mixture was dissolved in dichloromethane and washed with water for four

times. The organic layer was dried over anhydrous Magnesium sulfate. After filtration and concentration, flash chromatography (silica gel, elution with 5% ether in CH2Cl2) then afforded the title compound (28.8 mg, 0.092 mmol, 41%) as a brown solid. The free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the final title compound as a white solid. m/z 313.1 [M+1] for free base.

Example 80

Preparation of (2-Ethylsulfanyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidin-4-yl)-indan-2-yl-amine, hydrochloride.



(i) (2-Ethylsulfanyl-7,8-dihydro-3H,6H-pyrano[3,2-d]pyrimidin-4-one)

To a solution of sodium carbonate (powder, 2.00 g, 18.9 mmol) in ethanol (24.8 mL) was added *S*-ethylisothiourea hydrogen bromide (2.51 g, 15.7 mmol). The mixture was stirred at room temperature for 15 min, while a solution of ethyl 3-oxotetrahydropyran-2-carboxylate (10.4 mmol) in ethanol (10 mL) was added in a dropwise fashion. The mixture was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo. Water and dichloromethane were added. The pH was adjusted to 6 by addition of acetic acid. The aqueous layer was extracted with dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The

residue was subjected to next reaction without any purification. m/z 213.0 [M+1].

(ii) 4-Chloro-2-ethylsulfanyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidine

The above 2-ethylsulfanyl-7,8-dihydro-3H,6H-pyrano[3,2-d]pyrimidin-4-one was mixed with phosphorus oxychloride (5.2 mL). The mixture was heated to reflux for 2h. The mixture was cooled to room temperature and concentrated in vacuo to remove the excess of reagent. After dilution with dichloromethane, the resulted dark solution was added dropwise slowly with stirring into a mixture of saturated sodium bicarbonate solution with some ice. The mixture was then extracted with dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Silica gel, elution with ether and dichloromethane in hexanes 40:64:500) to afford the intermediate title as a light brown solid. (205 mg, 0.890 mmol, 9% for 2 steps). m/z 231.0 [M+1].

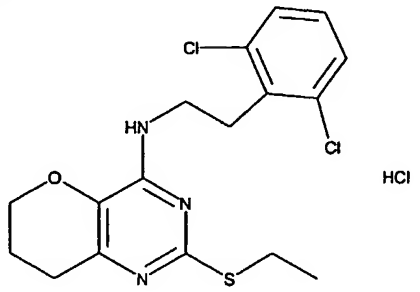
(iii) (2-Ethylsulfanyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidin-4-yl)-indan-2-yl-amine

To a solution of 4-chloro-2-ethylsulfanyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidine (100 mg, 0.434 mmol) in anhydrous NMP (0.80 mL) was added 2-aminoindane hydrochloride (224 mg, 1.30 mmol). To this solution was added diisopropylethylamine (242 mg, 0.38 mL, 2.2 mmol) dropwise slowly and at room temperature. The mixture was then heated at 50 degree for 16 hours. Water (50 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica

gel, gradient elution with 30% ether in hexanes) then afforded the title compound (64 mg, 68%) as a brown solid. The free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the final title compound as a white solid. m/z 328.1 [M+1] for free base.

Example 81

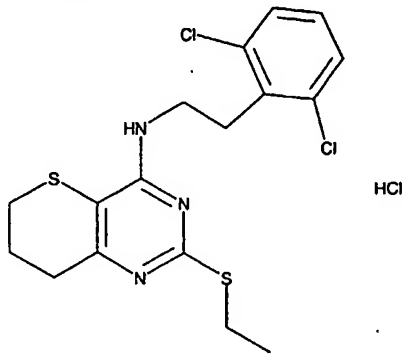
Preparation of [2-(2,6-Dichloro-phenyl)-ethyl]-(2-ethylsulfanyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidin-4-yl)-amine hydrochloride.



To a solution of 4-chloro-2-ethylsulfanyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidine (132 mg, 0.578 mmol) in anhydrous NMP (1.06 mL) was added 2-(2,6-dichlorophenyl)ethylamine (328 mg, 1.72 mmol). The mixture was then heated at 50 degree for 16 hours. Water (80 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, elution with ether:hexanes 1:2) then afforded the title compound (222 mg, 0.578 mmol, 100%) as a light yellow oil. The free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the title compound as a white solid. m/z 384.3 [M+1] for free base.

Example 82

Preparation of [2-(2,6-Dichloro-phenyl)-ethyl]-(2-ethylsulfanyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-yl)-amine, hydrochloride.



(i) 2-Ethylsulfanyl-7,8-dihydro-3H,6H-thiopyrano[3,2-d]pyrimidin-4-one

To a solution of sodium carbonate (powder, 454 mg, 4.28 mmol) in ethanol (3.0 mL) was added *S*-ethyl(isothiourea) hydrobromide (594 mg, 3.21 mmol). The mixture was stirred at room temperature for 15 min, while a solution of ethyl 3-thiatetrahydropyran-2-carboxylate (402 mg, 2.14 mmol) in ethanol (1.3 mL) was added in a dropwise fashion. The mixture was stirred at room temperature for 16 hours. The mixture was concentrated in vacuo. Water and dichloromethane were added. The pH was adjusted to 6 by addition of acetic acid. The aqueous layer was extracted with dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was subjected to next reaction without any purification. m/z 226.9 [M-1].

(ii) 4-Chloro-2-ethylsulfanyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine

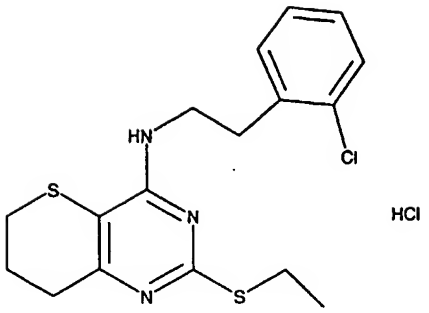
The above 2-ethylsulfanyl-7,8-dihydro-3H,6H-thiopyrano[3,2-d]pyrimidin-4-one was mixed with phosphorus oxychloride (2.0 mL). The mixture was heated to reflux for 2h. The mixture was cooled to room temperature and concentrated in vacuo to remove the excess of reagent. After dilution with

dichloromethane, the resulted dark solution was added dropwise slowly with stirring into a cold mixture of saturated sodium bicarbonate solution with some ice. The mixture was then extracted with dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Silica gel, elution with ether and dichloromethane in hexanes 1:1:5) to afford the intermediate title compound as a light brown solid. (309 mg, 1.26 mmol, 59% for 2 steps). m/z 246.9 [M+1].

(iii) To a solution of 4-chloro-2-ethylsulfanyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine (150 mg, 0.610 mmol) in anhydrous NMP (1.13 mL) was added 2-(2,6-dichlorophenyl)ethylamine (348 mg, 1.83 mmol). The mixture was then heated at 50 degree for 16h. Water (80 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, elution with ether:hexane 1:2.5) then afforded the desired product (237 mg, 0.593 mmol, 97%) as a brown solid. The free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the final title compound as a white solid. m/z 400.0 [M+1].

Example 83

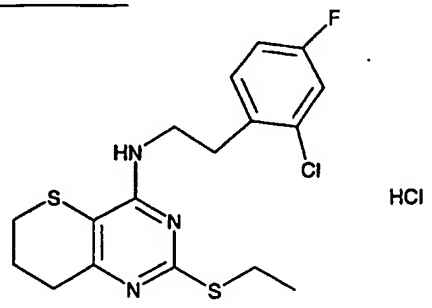
Preparation of [2-(2-Chloro-phenyl)-ethyl]-(2-ethylsulfanyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-yl)-amine, hydrochloride.



To a solution of 4-chloro-2-ethylsulfanyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine (158 mg, 0.642 mmol) in anhydrous NMP (1.20 mL) was added 2-(2-chlorophenyl)ethylamine (300 mg, 1.93 mmol). The mixture was then heated at 90 degree for 16h. Water (80 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, elution with ether:dichloromethane:hexane 1:1:2.5) then afforded the desired product (202 mg, 0.554 mmol, 86%) as a brown solid. The free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the title compound as a white solid. m/z 365.8 [M+1].

Example 84

Preparation of [2-(2-Chloro-4-fluoro-phenyl)-ethyl]-(2-ethylsulfanyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-yl)-amine, hydrochloride.



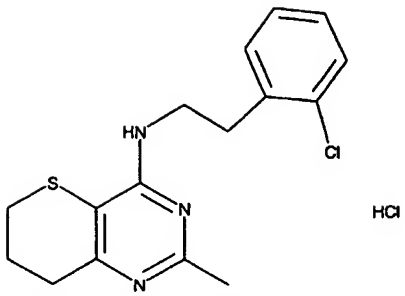
2-(2-chloro-4-fluorophenyl)ethylamine hydroacetate.

To a solution of 2-chloro-4-fluorobenzylcyanide (3.02 g, 17.8 mmol) in acetic acid (100 mL) was added platinum (IV) oxide (0.377 g). The mixture was stirred at room temperature under H2 (60 psi) for 6 hours. The solvent was removed in vacuo and the mixture was dissolved in ether and filtered. The filtrate was combined with toluene and concentrated in vacuo to give the intermediate title compound (3.16 g, 76%) as a white solid. m/z 174.2 [M+1].

To a solution of 4-chloro-2-ethylsulfanyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine (123 mg, 0.500 mmol) in anhydrous NMP (0.80 mL) was added 2-(2-chloro-4-fluorophenyl)ethylamine hydroacetate (233 mg, 1.00 mmol). To this solution was added diisopropylethylamine (323 mg, 0.44 mL, 2.5 mmol) dropwise slowly and at room temperature. The mixture was then heated at 90 degree for 16 hours. Water (60 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, elution with 30% ether in hexanes) then afforded the desired free base (166 mg, 87%) as a brown solid. The free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the final title compound as a white solid. m/z 384.2 [M+1] for free base.

Example 85

Preparation of [2-(2-Chloro-phenyl)-ethyl]-(2-methyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-yl)-amine, hydrochloride.



(i) 2-Methyl-7,8-dihydro-3H,6H-thiopyrano[3,2-d]pyrimidin-4-one.

To a solution of sodium ethoxide (456 mg, 6.69 mmol) in ethanol (6.60 mL) was added acetamidine hydrochloride (633 mg, 6.69 mmol). The mixture was stirred at room temperature for 15 min, while a solution of ethyl 3-oxotetrahydropyran-2-carboxylate (898 mg, 4.78 mmol) in ethanol (3.0 mL) was added in a dropwise fashion. The mixture was heated at reflux for 16 hours. The mixture was concentrated in vacuo. Water and dichloromethane were added. The pH was adjusted to 6 by addition of acetic acid. The aqueous layer was extracted with dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue (0.90 g) was subjected to next reaction without any purification. m/z 182.8 [M+1].

(ii) 4-Chloro-2-methyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine

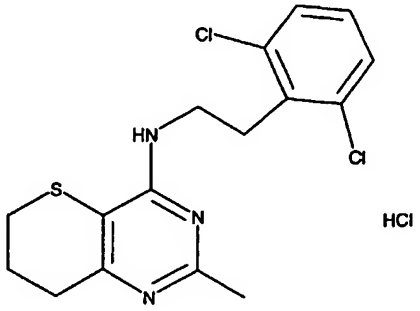
The above 2-methyl-7,8-dihydro-3H,6H-thiopyrano[3,2-d]pyrimidin-4-one (0.90 g) was mixed with phosphorus oxychloride (5.0 mL). The mixture was heated to reflux for 2h. The mixture was cooled to room temperature and concentrated in vacuo to remove the excess of reagent. After dilution with dichloromethane, the resulted dark solution was added dropwise slowly with stirring into a mixture of saturated sodium bicarbonate solution with some ice. The mixture was then extracted with dichloromethane

for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Silica gel, elution with ether and dichloromethane in hexanes 1:2:4) to afford the intermediate title compound as a light brown solid. (581 mg, 2.91 mmol, 61% for 2 steps). m/z 200.8 [M+1].

(iii) To a solution of 4-chloro-2-methyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine (215 mg, 1.08 mmol) in anhydrous NMP (2.0 mL) was added 2-(2-chlorophenyl)ethylamine (502 mg, 3.23 mmol). The mixture was then heated at 90 degree for 16 hours. Water (50 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, elution with EtOAc:dichloromethane 1:1.2) then afforded the desired free base (296 mg, 0.928 mmol, 86%) as a brown solid. The free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the final title compound as a white solid. m/z 320.1 [M+1] for free base.

Example 86

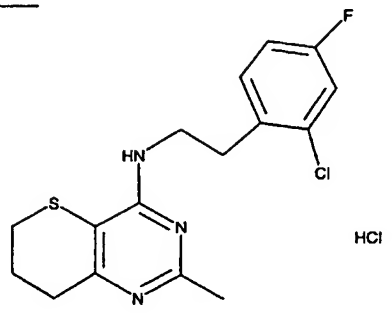
Preparation of [2-(2,6-Dichloro-phenyl)-ethyl]-(2-methyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-yl)-amine, hydrochloride.



To a solution of 4-chloro-2-methyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine (215 mg, 1.08 mmol) in anhydrous NMP (2.0 mL) was added 2-(2,6-dichlorophenyl)ethylamine (613 mg, 3.23 mmol). The mixture was then heated at 90 degree for 16 hours. Water (50 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, elution with ether:dichloromethane 1:1) then afforded the desired free base (346 mg, 0.980 mmol, 91%) as a brown solid. The free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the title compound as a white solid. m/z 354.0 [M+1] for free base.

Example 87

Preparation of [2-(2-Chloro-4-fluoro-phenyl)-ethyl]-(2-methyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-yl)-amine, hydrochloride.

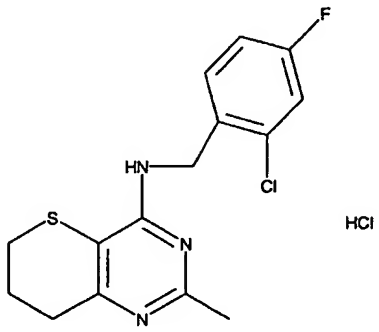


To a solution of 4-chloro-2-methyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine (200 mg, 1.00 mmol) in anhydrous NMP (1.60 mL) was added 2-(2-chloro-4-fluorophenyl)ethylamine hydroacetate (466 mg, 2.00 mmol). To this solution was added diisopropylethylamine (647 mg, 0.872 mL, 5.0 mmol) dropwise slowly and at room temperature. The mixture was then heated at 90 degree for 16 hours. Water (80 mL) and dichloromethane were added to quench the

reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, elution with ether:hexanes 1:2) then afforded the desired free base (311 mg, 0.92 mmol, 92%) as a brown solid. The free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the title compound as a white solid. m/z 338.3 [M+1] for free base.

Example 88

Preparation of (2-Chloro-4-fluoro-benzyl)-(2-methyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-yl)-amine, hydrochloride.

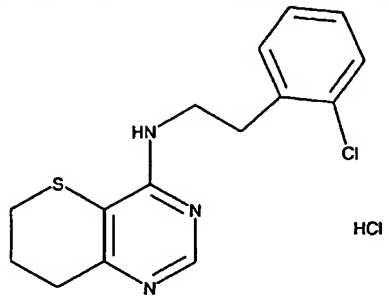


To a solution of 4-chloro-2-methyl-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine (165 mg, 0.823 mmol) in anhydrous NMP (1.60 mL) was added 2-chloro-4-fluorobenzylamine (438 mg, 2.47 mmol). The mixture was then heated at 90 degree for 16 hours. Water (80 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, elution with 10% MeOH in EtOAc) then afforded the desired free base (195 mg, 0.60 mmol, 72%) as a brown solid. The free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the

resulting solution was evaporated to give the title compound as a white solid. m/z 324.2 [M+1] for free base.

Example 89

Preparation of [2-(2-Chloro-phenyl)-ethyl]-(7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidin-4-yl)-amine, hydrochloride.



(i) 7,8-Dihydro-3H,6H-thiopyrano[3,2-d]pyrimidin-4-one

To a solution of sodium ethoxide (408 mg, 0.898 mmol) in ethanol (5.55 mL) was added formamidine acetate (623 mg, 6.00 mmol). The mixture was stirred at room temperature for 15 min, while a solution of ethyl 3-oxotetrahydropyran-2-carboxylate (898 mg, 4.78 mmol) in ethanol (3.0 mL) was added in a dropwise fashion. The mixture was heated at reflux for 16 hours. The mixture was concentrated in vacuo. Water and dichloromethane were added. The pH was adjusted to 6 by addition of acetic acid. The aqueous layer was extracted with dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was subjected to next reaction without any purification. m/z 168.9 [M+1].

(ii) 4-Chloro-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine

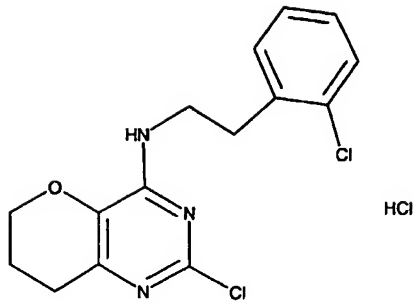
The above 7,8-dihydro-3H,6H-thiopyrano[3,2-d]pyrimidin-4-one was mixed with phosphorus oxychloride (5.0 mL). The mixture was heated to reflux for 2h. The mixture was cooled to room temperature and concentrated in vacuo to remove the excess of reagent. After dilution with dichloromethane, the

resulted dark solution was added dropwise slowly with stirring into a mixture of saturated sodium bicarbonate solution with some ice. The mixture was then extracted with dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Silica gel, elution with ether and dichloromethane in hexanes 1:2:4) to afford the intermediate title compound as a light brown solid. (336 mg, 1.81 mmol, 38% for 2 steps). m/z 187.0 [M+1].

(iii) To a solution of 4-chloro-7,8-dihydro-6H-thiopyrano[3,2-d]pyrimidine (136 mg, 0.731 mmol) in anhydrous NMP (1.37 mL) was added 2-(2-chlorophenyl)ethylamine (341 mg, 2.19 mmol). The mixture was then heated at 90 degree for 16 hours. Water (50 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, elution with 45% EtOAc in dichloromethane) then afforded the desired free base (205 mg, 0.673 mmol, 92%) as a brown solid. The free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the final title compound as a white solid. m/z 305.8 [M+1] for free base.

Example 90

Preparation of (2-Chloro-7,8-dihydro-6H-pyrano[3,2-d]pyrimidin-4-yl)-[2-(2-chloro-phenyl)-ethyl]-amine, hydrochloride.



(i) [2-(2-Chloro-phenyl)-ethyl]-(2-methylsulfanyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidin-4-yl)-amine

To a solution of 4-chloro-2-methylsulfanyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidine (85 mg, 0.394 mmol) in anhydrous NMP (1.0 mL) was added 2-(2-chlorophenyl)ethylamine (123 mg, 0.787 mmol). The mixture was then heated at 90 degree for 16 hours. Water (50 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, elution with ether and dichloromethane in hexanes 1:1:2) then afforded the intermediate title compound (79.1 mg, 0.225 mmol, 57%) as a brown solid. m/z 352.1 [M+1].

(ii) 4-[2-(2-Chloro-phenyl)-ethylamino]-7,8-dihydro-6H-pyrano[3,2-d]pyrimidin-2-ol

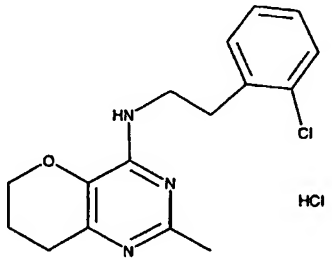
The above methyl sulfide (20.5 mg, 0.0584 mmol) was dissolved in acetic acid (0.5 mL). Hydrogen peroxide (30% aqueous solution, 0.027 mL, 0.234 mmol) was added. The mixture was heated at 140 degree for 1 hour. Aqueous workup afforded the desired intermediate title compound(15 mg, 0.049 mmol, 84%) as a light yellow oil. m/z 306.0 [M+1].

(iii) The above crude 2-hydroxy aminopyrimidine (15 mg, 0.049 mmol) was mixed with phosphorus oxychloride (1.0 mL).

The mixture was heated to reflux for 2h. The mixture was cooled to room temperature and concentrated in vacuo to remove the excess of reagent. After dilution with dichloromethane, the resulted dark solution was added dropwise slowly with stirring into a mixture of saturated sodium bicarbonate solution with some ice. The mixture was then extracted with dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Silica gel, elution with ether and dichloromethane in hexanes 30:40:100) to afford the final title compound as a light brown solid. (6.3 mg, 0.0195 mmol, 40%). m/z 340.0 [M+1].

Example 91

Preparation of [2-(2-Chloro-phenyl)-ethyl]-(2-methyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidin-4-yl)-amine, hydrochloride.



(i) 4-Hydroxy-2-Methyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidine

To a solution of sodium ethoxide (638 mg, 9.38 mmol) in ethanol (10.0 mL) was added acetamidine hydrochloride (887 mg, 9.38 mmol). The mixture was stirred at room temperature for 15 min, while a solution of ethyl 3-oxotetrahydropyran-2-carboxylate (6.70 mmol) in ethanol (3.0 mL) was added in a dropwise fashion. The mixture was heated at reflux for 16 hours. The mixture was concentrated in vacuo. Water and dichloromethane were added. The pH was adjusted to 6 by addition of acetic acid. The aqueous layer was extracted

with dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue (632 mg) was subjected to next reaction without any purification. m/z 167.0 [M+1].

(ii) 4-Chloro-2-methyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidine

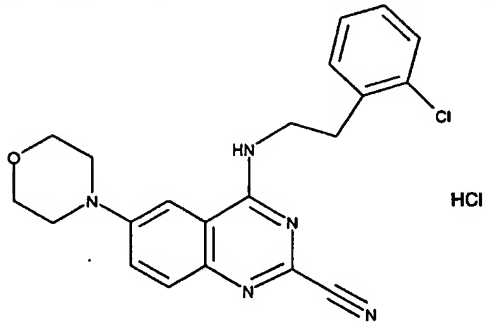
The above 4-hydroxy-2-Methyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidine (632 mg, 6.70 mmol) was mixed with phosphorus oxychloride (7.0 mL). The mixture was heated to reflux for 2h. The mixture was cooled to room temperature and concentrated in vacuo to remove the excess of reagent. After dilution with dichloromethane, the resulted dark solution was added dropwise slowly with stirring into a mixture of saturated sodium bicarbonate solution with some ice. The mixture was then extracted with dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (silica gel, elution with 13% ether in dichloromethane) to afford the intermediate title compound as a light brown solid. (271 mg, 1.61 mmol, 22% for 2 steps). m/z 185.0 [M+1].

(iii) To a solution of 4-chloro-2-methyl-7,8-dihydro-6H-pyrano[3,2-d]pyrimidine (298 mg, 1.61 mmol) in anhydrous NMP (3.26 mL) was added 2-(2-chlorophenyl)ethylamine (502 mg, 3.23 mmol). The mixture was then heated at 90 degree for 16 hours. Water (50 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, elution with acetone and dichloromethane in hexanes 1:1:1) then afforded the desired free base (268 mg, 0.885 mmol, 55%) as a brown solid. The

free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the final title compound as a white solid. m/z 304.1 [M+1] for free base.

Example 92

Preparation of 4-[2-(2-Chloro-phenyl)-ethylamino]-6-morpholin-4-yl-quinazoline-2-carbonitrile, hydrochloride.



(i) 6-Iodo-quinazoline-2,4-diol

To a solution of 2-amino-5-iodo-benzoic acid (10.0 g, 38.02 mmol) in NMP (150 mL) was added urea (4.56 g, 76.04 mmol). The mixture was heated at 230 degree for 20 hours. Water (300 mL) was added to form the black fine solid. The mixture was stirred for 1 hour, then filtered. The dark brown solid was then dried in vacuum oven for overnight at 70 degree to give the intermediate title compound (4.95 g, 45%). m/z 288.0 [M].

(ii) 2,4-Dichloro-6-iodo-quinazoline

The above 6-iodo-quinazoline-2,4-diol (4.95 g, 17.2 mmol) was mixed with phosphorus oxychloride (68 mL). The mixture was heated to reflux for 24h. The mixture was cooled to room temperature and concentrated in vacuo to remove the excess of reagent. After dilution with dichloromethane, the resulted dark solution was added dropwise slowly with stirring into a mixture of saturated sodium bicarbonate solution with some ice. The mixture was then extracted with

dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was purified by flash chromatography (Silica gel, elution with 30% EtOAc in hexanes) to afford the intermediate title compound as a light brown solid. (4.17 g, 75%). m/z 326.0 [M+1].

(iii) (2-Chloro-6-iodo-quinazolin-4-yl)-[2-(2-chloro-phenyl)-ethyl]-amine

To a solution of 2,4-dichloro-6-iodo-quinazoline (4.17g, 12.8 mmol) in anhydrous NMP (35.6 mL) was added 2-(2-chlorophenyl)ethylamine (2.35 mL, 16.7 mmol) and diisopropylethylamine (4.47 mL, 25.7 mL). The mixture was then heated at 90 degree for 16 hours. Water was added to quench the reaction. The solid crushed out. The mixture was then mixed with 1:1 ether/Hexanes, and stirred for 2h, then filtered. The solid was collected and dried in vacuum oven at 60 degree overnight to give the intermediate title compound as light yellow solid. (2.12 g, 90%) m/z 443.9 [M+1].

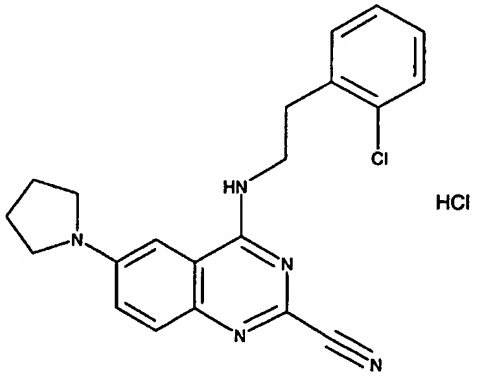
(iii) 4-[2-(2-Chloro-phenyl)-ethylamino]-6-iodo-quinazoline-2-carbonitrile

To a solution of the above 2-chloropyrimidine (4.59 g, 10.3 mmol) in DMSO (52 mL) was added potassium cyanide (6.72 g, 103.3 mmol). The mixture was heated to 120 degree for 72 hours. The mixture was dissolved in dichloromethane and washed with water for four times. The organic layer was dried over anhydrous Magnesium sulfate. After filtration and concentration, flash chromatography (silica gel, elution with 20% EtOAc in hexanes) then afforded the intermediate title compound (2.94 g, 63%) as a brown solid. m/z 435.0 [M+1].

(iv) To a solution of the above 4-[2-(2-chloro-phenyl)-ethylamino]-6-iodo-quinazoline-2-carbonitrile (50 mg, 0.115 mmol) in DMF (0.77 mL) was added $Pd_2(dba)_3$ (5.5 mg, 0.012 mmol), t-BuONa (26 mg, 0.27 mmol) and BINAP (11 mg, 0.035 mmol). The mixture was degassed for 20 min. Morpholine (20.0 mg, 0.23 mmol) was added. The mixture was heated at 90 degree for 16 hours. Water (50 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, elution with EtOAc and dichloromethane in hexanes 15:10:30) then afforded the desired free base (30 mg, 0.0763 mmol, 66%) as a brown solid. The free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the final title compound as a white solid. m/z 394.1 [M+1] for free base.

Example 93

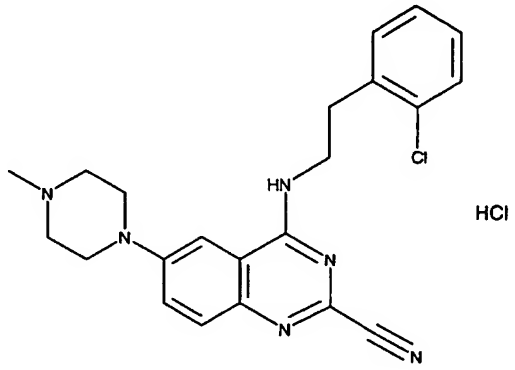
Preparation of 4-[2-(2-Chloro-phenyl)-ethylamino]-6-pyrrolidin-1-yl-quinazoline-2-carbonitrile, hydrochloride.



Prepared in a manner analogous to the procedure outlined for example 92. 53% yield, m/z 378.2 [M+1] for free base.

Example 94

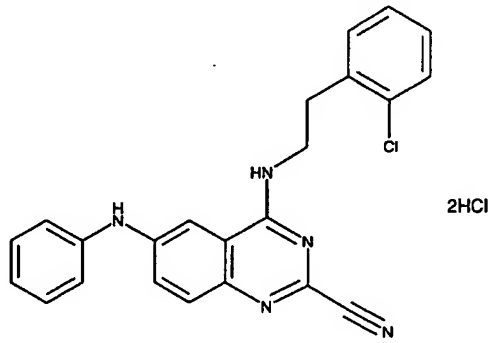
Preparation of 4-[2-(2-Chloro-phenyl)-ethylamino]-6-(4-methyl-piperazin-1-yl)-quinazoline-2-carbonitrile, hydrochloride.



Prepared in a manner analogous to the procedure outlined for example 92. 51% yield, m/z 407.2 [M+1] for free base.

Example 95

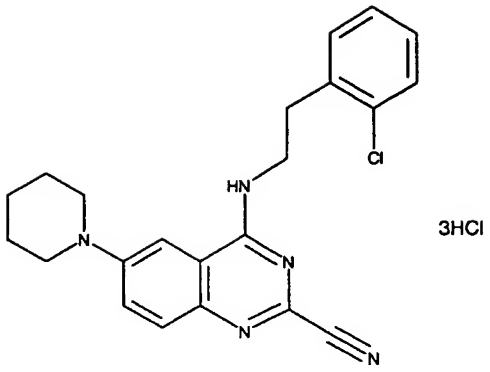
Preparation of 4-[2-(2-Chloro-phenyl)-ethylamino]-6-phenylamino-quinazoline-2-carbonitrile, dihydrochloride.



Prepared in a manner analogous to the procedure outlined for example 92. 33% yield, m/z 400.1 [M+1] for free base.

Example 96

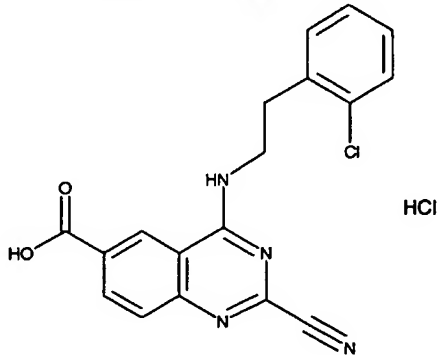
Preparation of 4-[2-(2-Chloro-phenyl)-ethylamino]-6-piperidin-1-yl-quinazoline-2-carbonitrile, trishydrochloride.



Prepared in a manner analogous to the procedure outlined for example 92. 42% yield, m/z 392.2 [M+1] for free base.

Example 97

Preparation of 4-[2-(2-Chloro-phenyl)-ethylamino]-2-cyano-quinazoline-6-carboxylic acid, hydrochloride.



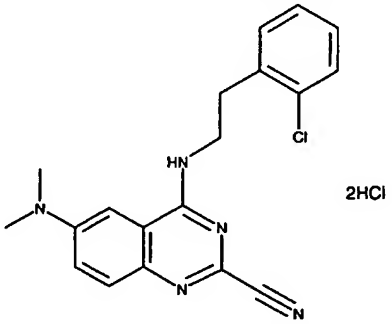
(i) 4-[2-(2-Chloro-phenyl)-ethylamino]-2-cyano-quinazoline-6-carboxylic acid methyl ester

2-Cyano-4-(2-chlorophenyl)ethylamino-6-iodopyrimidine (248 mg, 0.571 mmol) was dissolved in MeOH (10 mL), acetonitrile (25 mL) and triethylamine (1 mL). $PdCl_2(PPh_3)_2$ (15.0 mg) was added. The mixture was heated at 60 degree under CO (60 psi) for 24 h. The solvent was removed in vacuo. The residue was purified by flash chromatography (silica gel, elution with 50% EtOAc in hexanes) to afford the desired methyl ester (69.0 mg, 33%) as a off-white solid. m/z 367.1 [M+1]

(ii) To a solution of the above 4-[2-(2-chloro-phenyl)-ethylamino]-6-iodo-quinazoline-2-carbonitrile (46.7 mg, 0.128 mmol) in THF (2.0 mL) was added aqueous LiOH solution (0.3 M, 0.54 mL, 0.161 mmol) at 0 degree. The mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo. The residue was purified by flash chromatography (silica gel, elution with 13% MeOH in dichloromethane) to afford the desired carboxylic acid (34 mg, 0.966 mmol, 75%) as a white foam. The product was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the title compound as a white solid. m/z 353.1 [M+1] for the acid.

Example 98

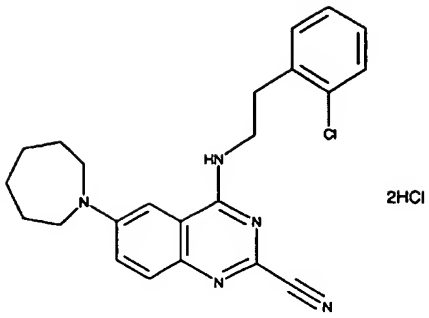
Preparation of 4-[2-(2-Chloro-phenyl)-ethylamino]-6-dimethylamino-quinazoline-2-carbonitrile, bishydrochloride.



Prepared in a manner analogous to the procedure outlined for example 92. 51% yield, m/z 352.1 [M+1] for free base.

Example 99

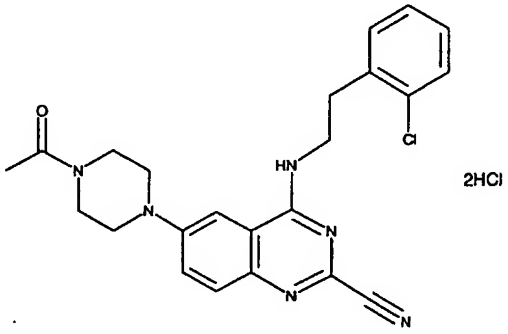
Preparation of 6-Azepan-1-yl-4-[2-(2-chloro-phenyl)-ethylamino]-quinazoline-2-carbonitrile, bishydrochloride.



Prepared in a manner analogous to the procedure outlined for example 92. 62% yield, m/z 406.2 [M+1] for free base.

Example 100

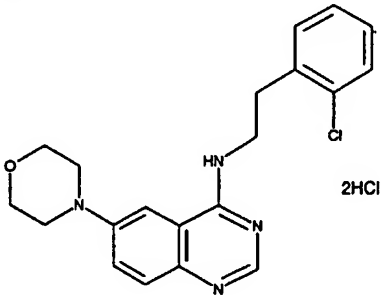
Preparation of 6-(4-Acetyl-piperazin-1-yl)-4-[2-(2-chloro-phenyl)-ethylamino]-quinazoline-2-carbonitrile, bishydrochloride.



Prepared in a manner analogous to the procedure outlined for example 92. 73% yield, m/z 435.2 [M+1] for free base.

Example 101

[2-(2-Chloro-phenyl)-ethyl]-(6-morpholin-4-yl-quinazolin-4-yl)-amine, bishydrochloride.



(1) 6-Iodo-quinazolin-4-ol

A solution of 2-amino-5-iodo-benzoic acid (5.0 g, 19.0 mmol) in formamide (21.6 g, 479 mmol) was heated at 160 degree for 3 hours. Water (50 mL) was added to form the black fine solid. The mixture was stirred for 16 hour, then filtered to collect the solid. The dark brown solid was then dried in vacuum oven for overnight at 60 degree to give the intermediate title compound (4.83 g, 94%), m/z 273.0 [M+1].

(ii) 4-Chloro-6-iodo-quinazoline

The above 6-iodo-quinazolin-4-ol (4.83 g, 17.8 mmol) was mixed with phosphorus oxychloride (34.1 mL). The mixture was heated to reflux for 2.5 h. The mixture was cooled to room temperature and concentrated in vacuo to remove the excess of reagent. After dilution with dichloromethane, the resulted dark solution was added dropwise slowly with stirring into a mixture of saturated sodium bicarbonate solution with some ice. The mixture was then extracted with dichloromethane for three times. The combined organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The residue was recrystallized in ether and collected by filtration to afford the intermediate title compound as a light brown solid. (4.56 g, 86%). m/z 287.0 [M+1].

(iii) [2-(2-Chloro-phenyl)-ethyl]-(6-iodo-quinazolin-4-yl)-amine

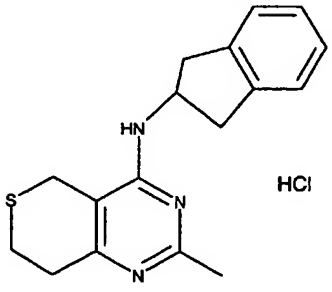
To a solution of 4-chloro-6-iodopyrimidine (2.5 g, 8.62 mmol) in anhydrous NMP (21.0 mL) was added 2-(2-chlorophenyl)ethylamine (1.58 mL, 11.2 mmol) and diisopropylethylamine (3.0 mL, 17.3 mL). The mixture was then heated at 50 degree for 18 hours. Water was added to quench the reaction. The solid crushed out. The mixture was then filtered with ether wash. The solid was collected and dried in vacuum oven at 60 degree overnight to give the

intermediate title compound as light yellow solid. (2.33 g, 5.71 mmol, 66%) m/z 410.1 [M+1].

(iv) To a solution of [2-(2-chloro-phenyl)-ethyl]-(6-iodo-quinazolin-4-yl)-amine (409 mg, 1.00 mmol) in DMF (6.50 mL) was added $Pd_2(dba)_3$ (45.8 mg, 0.05 mmol), BINAP (93.4 mg, 0.035 mmol) and t-BuONa (225 mg, 0.27 mmol). The mixture was degassed for 20 min. Morpholine (174 mg, 2.0 mmol) was added. The mixture was heated at 90 degree for 16 hours. Water (50 mL) and dichloromethane were added to quench the reaction. The mixture was then extracted with water for four times to remove NMP solvent. The organic layer was dried over anhydrous Magnesium sulfate. Flash chromatography (silica gel, elution with EtOAc and dichloromethane in hexanes 15:10:30) then afforded the desired free base (279 mg, 0.760 mmol, 76%) as a brown solid. The free base was dissolved in ethanol, the required amount of 0.5 M ethanolic hydrogen chloride was added and the resulting solution was evaporated to give the final title compound as a white solid. m/z 369.2 [M+1] for free base.

Example 102

Preparation of Indan-2-yl-(2-methyl-7,8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidin-4-yl)-amine.



4-Oxo-tetrahydro-thiopyran-3-carboxylic acid methyl ester. A solution of tetrahydrothiopyran-4-one (14.1 g, 120 mmol) in 50 mL THF is added dropwise to a cold (-78°C) solution of

LDA that was generated by adding a 1.6 M hexane solution of *n*-BuLi (91 mL, 145 mmol) to diisopropylamine (14.7 g, 145 mmol) in 200 mL THF. The resultant yellow solution is stirred at -78°C for 0.5 h and methyl cyanoformate (10.4 mL, 145 mmol) was added dropwise and the solution was warmed to 0°C. After stirring for 0.5 h at 0°C the solution is poured into 200 mL saturated NH_4Cl, neutralized with 1N HCl to pH = 7 and extracted with ether (3 x 200 mL). The organic layers are combined and washed with H_2O (100 mL), brine (100 mL) dried with Na_2SO_4 and concentrated *in vacuo* to provide the crude product. The crude product was purified by flash chromatography on silica gel (gradient elution 10 to 25% EtOAc/Hexanes) to yield the intermediate title compound. MS (ES) 175 (M^+ +1).

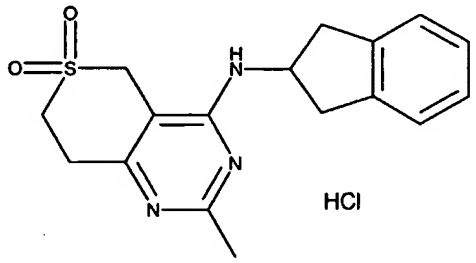
2-Methyl-7,8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidin-4-ol. Acetamidine hydrochloride (2.28 g, 24.1 mmol) is added to a solution of 4-Oxo-tetrahydro-thiopyran-3-carboxylic acid methyl ester (3.5 g, 20.1 mmol) and K_2CO_3 (13.9 g, 101 mmol) in 50 mL MeOH. After 4 h at room temperature the MeOH is removed *in vacuo* and the crude solid is neutralized (pH = 7) using 1N HCl followed by extraction with CH_2Cl_2 (3x75 mL). The organics are combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the intermediate title compound. MS (ES) 183 (M^+ +1).

Trifluoromethansulfonic anhydride (2.1 mL, 12.7 mmol) is added to a cool (0°C) solution of 2-Methyl-7,8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidin-4-ol (2.1 g, 11.5 mmol) and Et_3N (1.9 mL, 13.8 mmol) in 50 mL CH_2Cl_2 . After 0.5 h the solution is poured into H_2O followed by extraction with CH_2Cl_2 (3x75 mL). The organics are combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the pure triflate. The crude triflate (118 mg, 0.38 mmol) is

dissolved in 2.5 mL NMP and Hünig's base (0.14 mL, 0.83 mmol) is added followed by 2-aminoindane hydrochloride (76 mg, 0.45 mmol). The solution is heated to 90°C for 1h, cooled to RT, poured into H_2O (250 mL) and extracted with EtOAc (3x100 mL). The organics are combined and washed with H_2O (4x50 mL), brine (50 mL) dried with Na_2SO_4 and concentrated *in vacuo* to provide the crude product. The crude product was purified by flash chromatography on silica gel (eluent 75% EtOAc/Hexanes) to yield the final title compound. MS (ES) 298 (M^+ +1).

Example 103

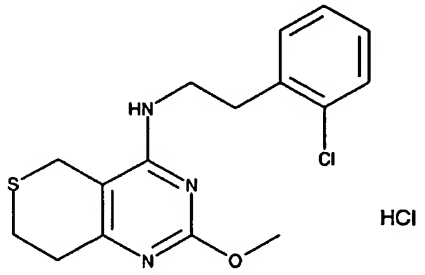
Preparation of Indan-2-yl-(2-methyl-6,6-dioxo-5,6,7,8-tetrahydro-6λ^6-thiopyrano[4,3-*d*]pyrimidin-4-yl)-amine hydrochloride.



m-CPBA (50 %) (0.12 g, 0.67 mmol) is added to a cool (0°C) solution of Indan-2-yl-(2-methyl-7,8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidin-4-yl)-amine (0.10 g, 0.34 mmol) in 2 mL CH_2Cl_2 . After 0.25 h the solution is poured into K_2CO_3 (sat) followed by extraction with EtOAc (3x10 mL). The organics are combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the free base of the title compound. MS (ES) 330 (M^+ +1). The free base is dissolved in a minimum amount of methylene chloride and an excess of a 1M solution of HCl in diethyl ether is added. The diethyl ether, methylene chloride and excess HCl are then removed in vacuo to produce the title compound.

Example 104

Preparation of [2-(2-Chloro-phenyl)-ethyl]-(2-methoxy-7,8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidin-4-yl)-amine hydrochloride.



2-Methoxy-7,8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidin-4-ol.

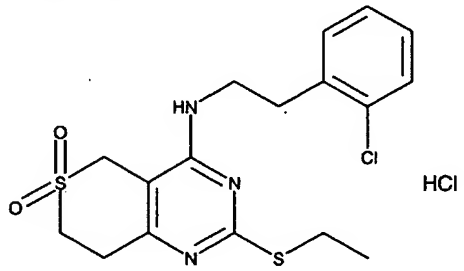
O-methylisourea hydrogen sulfate (1.2 g, 6.9 mmol) is added to a solution of 4-Oxo-tetrahydro-thiopyran-3-carboxylic acid methyl ester (1.0 g, 5.8 mmol) and K_2CO_3 (4.0 g, 29 mmol) in 20 mL MeOH. After 14 hrs at RT the MeOH is removed *in vacuo* and the crude solid is neutralized (pH = 7) using 1N HCl followed by extraction with CH_2Cl_2 (3x75 mL). The organics are combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the intermediate title compound. MS (ES) 199 (M^+ +1).

Trifluoromethansulfonic anhydride (0.72 mL, 4.28 mmol) is added to a cool (0°C) solution of 2-Methoxy-7,8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidin-4-ol (0.77 g, 3.895 mmol) and Et_3N (0.65 mL, 4.67 mmol) in 10 mL CH_2Cl_2. After 1 h the solution is poured into H_2O followed by extraction with CH_2Cl_2 (3x25 mL). The organics are combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the triflate. The crude triflate (0.79 g, 2.39 mmol) is dissolved in 10 mL NMP and Hünig's base (0.5 mL, 2.87 mmol) is added followed by 2-(2-chlorophenyl)-ethylamine (0.45 g, 2.87 mmol). The solution is heated to 90°C for 1h and poured into H_2O (50 mL) and extracted with EtOAc (3x25 mL). The organics are combined and washed with H_2O (4x25 mL), brine (25 mL) dried with Na_2SO_4 and concentrated *in vacuo* to provide the crude

product. The crude product was purified by flash chromatography on silica gel (gradient elution 25 to 50% EtOAc/Hexanes) to yield the free base of the final title compound. MS (ES) 337 (M^+ +1). The free base is dissolved in a minimum amount of methylene chloride and an excess of a 1M solution of HCl in diethyl ether is added. The diethyl ether, methylene chloride and excess HCl are then removed in vacuo to produce the title compound.

Example 105

Preparation of [2-(2-Chloro-phenyl)-ethyl]-(2-ethylsulfanyl-6,6-dioxo-5,6,7,8-tetrahydro-6λ^6-thiopyrano[4,3-*d*]pyrimidin-4-yl)-amine hydrochloride.



1,1,4-Trioxo-hexahydro-1λ^6-thiopyran-3-carboxylic acid methyl ester.

m-CPBA (50 %) (3.97 g, 11.5 mmol) is added to a cool (0°C) solution of 4-Oxo-tetrahydro-thiopyran-3-carboxylic acid methyl ester (1.0 g, 5.75 mmol) in 20 mL CH_2Cl_2 . After 0.5 h the solution is poured into K_2CO_3 (sat) followed by extraction with EtOAc (3x50 mL). The organics are combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the intermediate title compound. MS (ES) 207 (M^+ +1).

2-Ethylsulfanyl-6,6-dioxo-5,6,7,8-tetrahydro-6λ^6-thiopyrano[4,3-*d*]pyrimidin-4-ol.

2-Ethyl-2-thiopseudourea hydrobromide (1.1 g, 6.0 mmol) is added to a solution of 1,1,4-Trioxo-hexahydro-1λ^6-thiopyran-3-carboxylic acid methyl ester (0.8 g, 5.0 mmol) and K_2CO_3

(3.45 g, 25.0 mmol) in 25 mL MeOH. After 24 hrs at RT the MeOH is removed in vacuo and the crude solid is neutralized (pH = 7) using 1N HCl followed by extraction with CH_2Cl_2 (3 x 75 mL). The organics are combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the intermediate title compound. MS (ES) 263 (M^+ +1).

Trifluoro-methanesulfonic acid 2-ethylsulfanyl-6,6-dioxo-5,6,7,8-tetrahydro-6λ^6-thiopyrano[4,3-*d*]pyrimidin-4-yl ester.

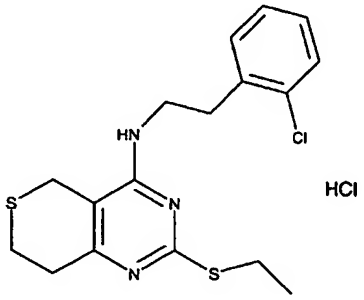
Trifluoromethansulfonic anhydride (0.47 mL, 2.81 mmol) is added to a cool (0°C) solution of 2-Ethylsulfanyl-6,6-dioxo-5,6,7,8-tetrahydro-6λ^6-thiopyrano[4,3-*d*]pyrimidin-4-ol (0.67 g, 2.56 mmol) and Et_3N (0.43 mL, 3.1 mmol) in 10 mL CH_2Cl_2. After 1 h the solution is poured into H_2O followed by extraction with CH_2Cl_2 (3x15 mL). The organics are combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the pure triflate. The crude product was purified by flash chromatography on silica gel (gradient elution 25 to 100% EtOAc/Hexanes) to yield the intermediate title compound. MS (ES) 392 (M^+ +1).

Trifluoromethanesulfonic acid 2-ethylsulfanyl-6,6-dioxo-5,6,7,8-tetrahydro-6λ^6-thiopyrano[4,3-*d*]pyrimidin-4-yl ester (100 mg, 0.25 mmol) is dissolved in 2.0 mL NMP and Hünig's base (0.05 mL, 0.31 mmol) is added followed by 2-(2-chlorophenyl)-ethylamine (48 mg, 0.31 mmol). The solution is heated to 90 °C for 2h and poured into H_2O (25 mL) and extracted with EtOAc (3x10 mL). The organics are combined and washed with H_2O (4x10 mL), brine (10 mL) dried with Na_2SO_4 and concentrated *in vacuo* to provide the crude product. The crude product was purified by flash chromatography on silica gel (eluent 50 % EtOAc/Hexanes) to yield the free base of the final title compound. MS (ES) 399

(M^+ +1). The free base is dissolved in a minimum amount of methylene chloride and an excess of a 1M solution of HCl in diethyl ether is added. The diethyl ether, methylene chloride and excess HCl are then removed in vacuo to produce the title compound.

Example 106

Preparation of [2-(2-Chloro-phenyl)-ethyl]-(2-ethylsulfanyl-7,8-dihydro-5H-thiopyrano[4,3-d]pyrimidin-4-yl)-amine hydrochloride.



2-Ethylsulfanyl-7,8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidin-4-ol.

2-Ethyl-2-thiopseudourea hydrobromide (0.22 g, 1.15 mmol) is added to a solution of 4-Oxo-tetrahydro-thiopyran-3-carboxylic acid methyl ester (0.18 g, 1.05 mmol) and K_2CO_3 (1.14 g, 8.25 mmol) in 10 mL MeOH. After 24 hrs at RT the MeOH is removed in vacuo and the crude solid is neutralized (pH = 7) using 1N HCl followed by extraction with CH_2Cl_2 (3x25 mL). The organics are combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the intermediate title compound. MS (ES) 229 (M^+ +1).

4-Chloro-2-ethylsulfanyl-7,8-dihydro-5H-thiopyrano[4,3-d]pyrimidine.

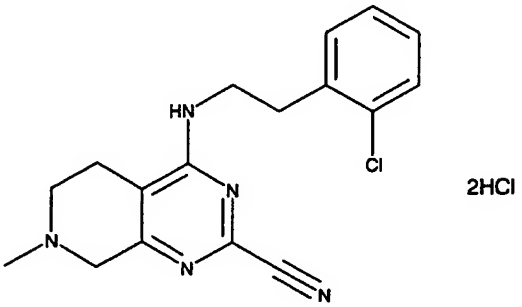
Phosphorus oxychloride (5 mL) is added 2-Ethylsulfanyl-7,8-dihydro-5*H*-thiopyrano[4,3-*d*]pyrimidin-4-ol (0.20 g, 0.88 mmol) and the resultant solution heated to 100°C. After 0.5 h the solution is cooled to RT and the excess phosphorus

oxychloride is removed *in vacuo* and H_2O is added. The solution is neutralized with K_2CO_3 (sat) to pH = 7 followed by extraction with EtOAc (3x25 mL). The organics are combined, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give the intermediate title compound. MS (ES) 246 (M^+ +1).

4-Chloro-2-ethylsulfanyl-7,8-dihydro-5H-thiopyrano[4,3-d]pyrimidine (170 mg, 0.69 mmol) is dissolved in 3.0 mL NMP and Hünig's base (0.10 mL, 0.69 mmol) is added followed by 2-(2-chlorophenyl)-ethylamine amine (129 mg, 0.82 mmol). The solution is heated to 110°C for 3 h, cooled to RT, poured into H_2O (25 mL) and extracted with EtOAc (3x20 mL). The organics are combined and washed with H_2O (4x10 mL), brine (10 mL) dried with Na_2SO_4 and concentrated *in vacuo* to provide the crude product. The crude product was purified by flash chromatography on silica gel (eluent 15 % EtOAc/Hexanes) to yield the free base of the final title compound. MS (ES) 366 (M^+ +1). The free base is dissolved in a minimum amount of methylene chloride and an excess of a 1M solution of HCl in diethyl ether is added. The diethyl ether, methylene chloride and excess HCl are then removed in vacuo to produce the final title compound.

Example 107

Preparation of 4-[2-(2-Chloro-phenyl)-ethylamino]-7-methyl-5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidine-2-carbonitrile bishydrochloride.



5-Hydroxy-4-(2-methyl-isothioureidocarbonyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester bishydrochloride.

To a solution of 4-Oxo-piperidine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (6.9 g, 25 mmol) in 100 mL H_2O and 20 mL THF at RT was first added sodium carbonate (13 g, 130 mmol) then 2-Methyl-2-thiopseudourea sulfate (7.1 g, 25 mmol). After stirring at RT for 3.5 h, the solution was neutralized to pH = 7 with aqueous HCl and aqueous NH_4Cl. The solution was then extracted with ethyl acetate (3x400 mL). The combined organic layers were washed with water (2x100 mL), brine (100 mL) dried with Na_2SO_4 and concentrated *in vacuo* to yield the intermediate title compound. MS (ES) 316 (M^+ +1).

4-Hydroxy-2-methylsulfanyl-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid *tert*-butyl ester.

A solution of 5-Hydroxy-4-(2-methyl-isothioureidocarbonyl)-3,6-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (0.48 g, 1.62 mmol) in 5 mL CH_2Cl_2 and 0.5 mL NMP was cooled to 0°C and triethylamine (0.35 mL, 2.52 mmol) was added, followed by trifluoromethane sulfonic anhydride (0.34 mL, 2.02 mmol). After stirring for 0.5 h., the solution was then poured into water and the crude product was extracted with ethyl acetate (3x500 mL). The combined organic layers were washed with water (2x250 mL), dried with Na_2SO_4, and concentrated *in vacuo* to provide the intermediate title compound. MS (ES) 298 (M^+ +1).

An alternative synthetic route to the intermediate title compound is as follows. To a solution of 4-Oxo-piperidine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (17.2 g, 67.2 mmol) in 200 mL dioxane and 400 mL toluene at RT was first added sodium carbonate (35.0 g, 335 mmol) then 2-methyl-2-thiopseudourea sulfate (22.4 g, 80.6 mmol).

After stirring at reflux temperature with azeotropic removal of water for 3.5 h, the solution was neutralized to pH = 7 with aqueous HCl. The solution was then extracted with ethyl acetate (3x400 mL). The combined organic layers were washed with water (2x100 mL), brine (100 mL) dried with Na_2SO_4 and concentrated *in vacuo* to yield the intermediate title compound. MS (ES) 298 (M^+ +1).

4-[2-(2-Chloro-phenyl)-ethylamino]-2-methylsulfanyl-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid *tert*-butyl ester.

A solution of 4-Hydroxy-2-methylsulfanyl-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid *tert*-butyl ester (7.5 g, 25 mmol) in 200 mL CH_2Cl_2 was cooled to 0°C and triethylamine (4.2 mL, 30 mmol) was added, followed by trifluoromethane sulfonic anhydride (4.7 mL, 28 mmol). After stirring for 0.5 h., the solution was then poured into water and the solution was extracted with ethyl acetate (3x500 mL). The combined organic layers were washed with water (2x250 mL), dried with Na_2SO_4, and concentrated *in vacuo* to provide the crude product that was then filtered through silica gel with CH_2Cl_2. To a solution of the triflate (4.0 g, 9.3 mmol) in NMP (40 mL) at RT was added *N,N*-diisopropylethylamine (2.0 mL, 11 mmol), and 2-(2-chlorophenyl)-ethylamine (1.4 mL, 10 mmol). After stirring overnight for 14 hrs, the solution was added to water and solution extracted with CH_2Cl_2 (3x500 mL). The combined organic layers were then washed with water (3x200 mL), dried with Na_2SO_4 and concentrated *in vacuo* to provide the crude product. The crude product was purified by flash chromatography on silica gel (eluent 20% EtOAc/Hexanes) to yield the intermediate title compound. MS (ES) 435 (M^+).

4-[2-(2-Chloro-phenyl)-ethylamino]-2-methanesulfonyl-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid *tert*-butyl ester.

To a solution of 4-[2-(2-Chloro-phenyl)-ethylamino]-2-methylsulfanyl-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid *tert*-butyl ester (11.3 g, 26.0 mmol) in CH_2Cl_2 (160 mL) at 0°C, was added *m*-CPBA (9.85 g, 57.1 mmol) in two consecutive equal portions. After stirring for 0.5 h, the solution was made basic (pH = 12) with aqueous NaOH and extracted with CH_2Cl_2 (2x500 mL). The combined organic layers were washed with water (2x200 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield the intermediate title compound. MS (ES) 467 (M^+).

4-[2-(2-Chloro-phenyl)-ethylamino]-2-cyano-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid *tert*-butyl ester.

To a solution of 4-[2-(2-Chloro-phenyl)-ethylamino]-2-methanesulfonyl-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid *tert*-butyl ester (10.1 g, 21.6 mmol) in NMP (100 mL) at RT was added KCN (14.1 g, 216 mmol), and the solution was then heated to 125 °C. After stirring for 20 h, the solution was added to water (1 L) and solution was extracted with CH_2Cl_2 (3x400 mL). The combined organic layers were then washed with water (4x200 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield crude product. The crude product was purified by flash chromatography on silica gel (eluent 50% EtOAc/Hexanes) to provide the intermediate title compound. MS (ES) 414 (M^+).

4-[2-(2-Chloro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidine-2-carbonitrile.

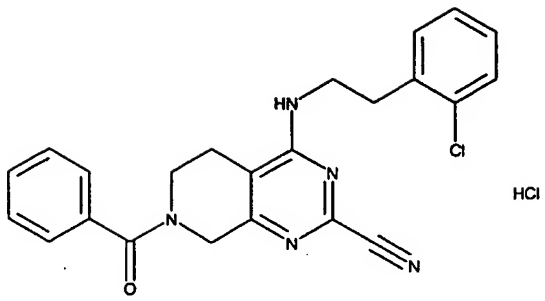
To a solution of 4-[2-(2-Chloro-phenyl)-ethylamino]-2-cyano-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic

acid *tert*-butyl ester (3.6 g, 8.7 mmol) in CH_2Cl_2 (60 mL) at 0°C, was added TFA (14 mL, 180 mmol). After warming to RT for 1 h, 2N NaOH was added to the solution until pH = 12. The crude product was then extracted with CH_2Cl_2 (2x200 mL). The combined organic layers were washed with water (2x100 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield the intermediate title compound. MS (ES) 314 (M^+).

To a solution of 4-[2-(2-Chloro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidine-2-carbonitrile (0.050 g, 0.16 mmol) in methanol (1 mL) at 0°C, was added formalin (9.5 mg, 0.32 mmol), then $NaBH(OAc)_3$ (0.050 g, 0.24 mmol). After 1 h, aqueous sodium bicarbonate (25 mL) was added to the solution and the solution was extracted with EtOAc (2x50 mL). The combined organic layers were washed with water (2x20 mL), brine (20 mL) dried with Na_2SO_4 and concentrated *in vacuo* to yield crude product. The crude product was purified by flash chromatography on HMDS treated silica gel with EtOAc to yield the free base of the final title compound. MS (ES) 328 (M^+). The free base is dissolved in a minimum amount of methylene chloride and an excess of a 1M solution of HCl in diethyl ether is added. The diethyl ether, methylene chloride and excess HCl are then removed in vacuo to produce the title compound.

Example 108

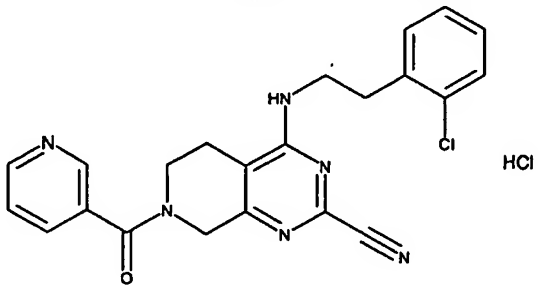
Preparation of 7-Benzoyl-4-[2-(2-chloro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidine-2-carbonitrile hydrochloride.



To a solution of 4-[2-(2-Chloro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidine-2-carbonitrile (0.050 g, 0.16 mmol) in CH_2Cl_2 (1 mL) at 0°C, was added pyridine (16 µL, 0.20 mmol), then benzoyl chloride(22 µL, 0.19 mmol). After 1.5 h, aqueous sodium bicarbonate (25 mL) was added to the solution. The solution was extracted with EtOAc (2x50 mL). The combined organic layers were washed with water (2x20 mL), brine (20 mL) dried with Na_2SO_4 and concentrated *in vacuo* to yield the crude product. The crude product was purified by flash chromatography (EtOAc) on silica gel to yield the free base of the title compound. MS (ES) 418 (M^+). The free base is dissolved in a minimum amount of methylene chloride and an excess of a 1M solution of HCl in diethyl ether is added. The diethyl ether, methylene chloride and excess HCl are then removed in vacuo to produce the title compound.

Example 109

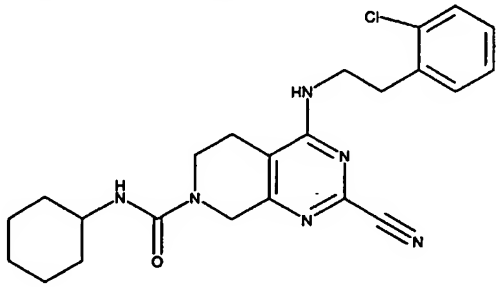
Preparation of 4-[2-(2-Chloro-phenyl)-ethylamino]-7-(pyridine-3-carbonyl)-5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidine-2-carbonitrile hydrochloride.



This compound was synthesized in a manner similar to Example 104, except in place of benzoyl chloride, nicotinoyl chloride (31 mg, 0.17 mmol) was used. The crude product was purified by flash chromatography on HMDS treated silica gel (10% MeOH/EtOAc) to yield the free base of the title compound. MS (ES) 419 (M^+). The free base is dissolved in a minimum amount of methylene chloride and an excess of a 1M solution of HCl in diethyl ether is added. The diethyl ether, methylene chloride and excess HCl are then removed in vacuo to produce the title compound.

Example 110

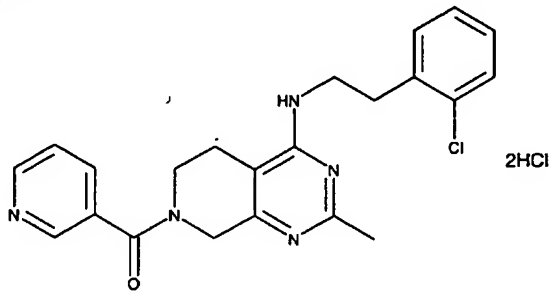
Preparation of 4-[2-(2-Chloro-phenyl)-ethylamino]-2-cyano-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid cyclohexylamide hydrochloride.



This compound was synthesized in a manner similar to Example 104, except in place of benzoyl chloride, cyclohexyl isocyanate (35 mg, 0.28 mmol) was used. The crude product was purified by flash chromatography on silica gel (10% MeOH/EtOAc) to yield the free base of the title compound. MS (ES) 440 (M^+ +1). The free base is dissolved in a minimum amount of methylene chloride and an excess of a 1M solution of HCl in diethyl ether is added. The diethyl ether, methylene chloride and excess HCl are then removed in vacuo to produce the title compound.

Example 111

Preparation of {4-[2-(2-Chloro-phenyl)-ethylamino]-2-methyl-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidin-7-yl}-pyridin-3-yl-methanone bishydrochloride.



4-Hydroxy-2-methyl-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid *tert*-butyl ester.

To a solution of 4-Oxo-piperidine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (5.0 g, 18 mmol) in 200 mL methanol at room temperature was added potassium carbonate (25 g, 180 mmol) then acetamidine hydrochloride (1.9 g, 20 mmol). After stirring at room temperature for 1 h, the solution was neutralized to pH = 7 with aqueous HCl and the solution was extracted with ethyl acetate (3x300 mL). The combined organic layers were washed with water (2x100 mL), dried with Na_2SO_4, and concentrated *in vacuo* to yield the intermediate title compound. MS (ES) 266 (M^+ +1).

2-Methyl-4-trifluoromethanesulfonyloxy-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid *tert*-butyl ester. A solution of 4-Hydroxy-2-methyl-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid *tert*-butyl ester (260 mg, 0.96 mmol) in 30 mL CH_2Cl_2 was cooled to 0°C and triethylamine (0.48 mL, 3.5 mmol) was added, followed by trifluoromethane sulfonic anhydride (0.48 mL, 2.9 mmol). After 10 minutes, the solution was quenched with water and the solution was extracted with CH_2Cl_2 (2x50 mL). The combined organic layers were washed with water (2x25 mL), dried with Na_2SO_4, and concentrated *in vacuo* to provide crude product. The crude product was purified by flash chromatography on silica gel (eluent 9% EtOAc/Hexanes) to yield the intermediate title compound. MS (ES) 398 (M^+ +1).

4-[2-(2-Chloro-phenyl)-ethylamino]-2-methyl-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid *tert*-butyl ester. To a solution of 2-Methyl-4-trifluoromethanesulfonyloxy-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid *tert*-butyl ester (310 mg, 0.79 mmol) in NMP (8.0 mL) at RT was added *N,N*- diisopropylethylamine (0.16 mL, 0.95 mmol), and 2-(2-chlorophenyl)-ethylamine (0.12 mL, 0.87 mmol). The solution was then heated to 80°C. After 2.5 h, the solution was poured into water and the solution was extracted with EtOAc (2x50 mL). The combined organic layers were then washed with water (2x25 mL), brine (3x20 mL), dried with Na_2SO_4 and concentrated *in vacuo* to provide the crude product. The crude product was purified by flash chromatography on silica gel (gradient elution 11→20% EtOAc/Hexanes) to yield the intermediate title compound. MS (ES) 403 (M^+).

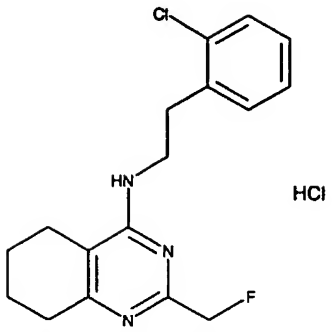
[2-(2-Chloro-phenyl)-ethyl]-(2-methyl-5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidin-4-yl)-amine.

To a solution of 4-[2-(2-Chloro-phenyl)-ethylamino]-2-methyl-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidine-7-carboxylic acid *tert*-butyl ester (5.6 g, 14 mmol) in CH_2Cl_2 (140 mL) at 0°C, was added TFA (40.0 mL, 520 mmol). After warming to room temperature for 1 h, 2N NaOH (40 mL) was added to the solution until pH 12 was reached. The solution was extracted with CH_2Cl_2 (2x500 mL) and the combined organic layers were washed with water (2x200 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield the intermediate title compound. MS (ES) 303 (M^+).

To a solution of [2-(2-Chloro-phenyl)-ethyl]-(2-methyl-5,6,7,8-tetrahydro-pyrido[3,4-*d*]pyrimidin-4-yl)-amine (0.050 g, 0.16 mmol) in CH_2Cl_2 (1 mL) at 0°C, was added pyridine (29 µL, 0.36 mmol), then nicotinoyl chloride hydrochloride (32 mg, 0.18 mmol). After 0.5 h, aqueous sodium bicarbonate (25 mL) was added to the solution and the solution was extracted with CH_2Cl_2 (2x50 mL). The combined organic layers were washed with water (2x20 mL), dried with Na_2SO_4 and concentrated *in vacuo* to yield the crude title product. The crude product was purified by flash chromatography on HMDS treated silica gel (5% MeOH/EtOAc) to yield the free base of the final title compound. MS (ES) 408 (M^+). The free base is dissolved in a minimum amount of methylene chloride and an excess of a 1M solution of HCl in diethyl ether is added. The diethyl ether, methylene chloride and excess HCl are then removed in vacuo to produce the title compound.

Example 112

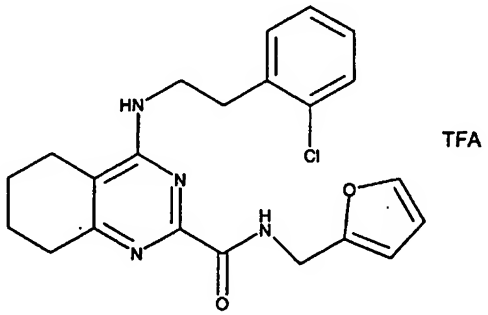
Preparation of [2-(2-Chloro-phenyl)-ethyl]-(2-fluoromethyl-5,6,7,8-tetrahydro-quinazolin-4-yl)-amine hydrochloride.



DAST (16.4 mg, 0.10 mmol) is added dropwise to a cold (-78°C) solution of {4-[2-(2-Chloro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-quinazolin-2-yl}-methanol (25.0 mg, 0.08 mmol) in 1 mL CH_2Cl_2. The solution is warmed to 0 °C over 3 h, poured into water (10 mL) and extracted with CH_2Cl_2 (3x10 mL). The organics are combined, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (gradient elution 10 to 25% EtOAc/Hexanes) to yield the free base of the title compound. MS (ES) 322 (M^+ +1). The free base is dissolved in a minimum amount of methylene chloride and an excess of a 1M solution of HCl in diethyl ether is added. The diethyl ether, methylene chloride and excess HCl are then removed in vacuo to produce the title compound.

Example 113

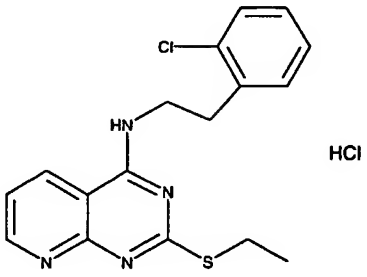
4-[2-(2-Chloro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-quinazoline-2-carboxylic acid (furan-2-ylmethyl)-amide trifluoroacetate.



A solution of EDCI (26.0 mg, 0.14 mmol) and HOBt (18.0 mg, 0.14 mmol) is added to 4-[2-(2-Chloro-phenyl)-ethylamino]-5,6,7,8-tetrahydro-quinazoline-2-carboxylic acid (50 mg, 0.14 mmol) in 1 mL DMF. Triethylamine (0.038 mL, 0.27 mmol) is added dropwise followed by 2-aminomethylfuran (0.014 mL, 0.16 mmol). After stirring for 16 h the solution was then poured into water and extracted with ethyl acetate (3x5 mL). The combined organic layers were washed with water (2x5 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel (gradient elution 25 to 50% EtOAc/Hexanes) to yield the free base of the title compound. MS (ES) 411 (M^+). The free base is dissolved in a minimum amount of methylene chloride and a slight excess of TFA (trifluoroacetic acid) is added. The methylene chloride and excess TFA is then removed under vacuum to provide the final title compound.

Example 114

Preparation of 2-Mercaptoethyl-4-[2-(2-chlorophenyl)ethylamino]pyrido(2,3-d) pyrimidine hydrochloride.



2-Chloro-4-hydroxypyrido(2,3-d) pyrimidine (1).

The intermediate titled compound was prepared essentially by the method outlined in *JACS*, 77, 2256 (1955).

2-Mercaptoethyl-4-chloropyrido(2,3-d) pyrimidine.

A mixture of 2-chloro-4-hydroxypyrido(2,3-d) pyrimidine (600 mg, 3.30 mmol), sodium ethanethiolate (960 mg, 11.60 mmol), and *N,N*-dimethylformamide (20 mL) was warmed at 85-95°C for

2 h. The solution was cooled, concentrated, and treated with 5% methanol in methylene chloride (25 mL). The resulting solid was dissolved in 1N HCl (50 mL), concentrated, and filtered with the aid of diethyl ether. The product was the hydrochloride salt of 2-mercaptoethyl-4-hydroxypyrido (2,3-d) pyrimidine, 1.5 g, and was used as such without further purification. MS (ES+) 208. The hydroxypyrimidine thus obtained (1.5 g, 3.30 mmol, containing sodium chloride) was refluxed in phosphorus oxychloride (20 mL) for 3 h. The reaction mixture was cooled, concentrated, and dissolved in chloroform (75 mL). The solution, containing some undissolved sodium chloride, was added slowly to an ice cold solution of saturated sodium bicarbonate (75 mL), the layers were separated, and the organic was backwashed with chloroform (25 mL). The combined organics were dried over sodium sulfate, concentrated, and purified by flash silica gel chromatography (ethyl acetate) to give a pale yellow solid of the intermediate title compound (613 mg, 82%). MS (ES+) 225.

Anal. Calcd for $C_9H_8N_3SCl$:
Theory: C, 47.90, H, 3.57, N, 18.62.
Found: C, 47.81, H, 3.42, N, 18.26.

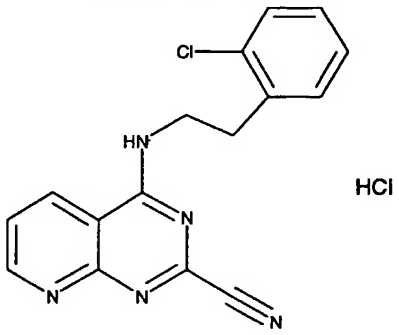
A mixture of 2-mercaptoethyl-4-chloropyrido(2,3-d) pyrimidine (152 mg, 0.67 mmol), 2-(2-chlorophenyl)ethylamine (133 mg, 0.86 mmol), potassium carbonate (186 mg, 1.35 mmol), and 1-methyl-2-pyrrolidinone (5 mL) was heated at 105-115 °C for 2 h. The reaction mixture was cooled and partitioned between ethyl acetate (40 mL) and water (40 mL). The organic layer was backwashed with brine (40 mL), dried over sodium sulfate, and concentrated to a residue. The residue was chromatographed over flash silica gel (ethyl acetate) to give the pure free base of the final title compound, 111 mg. The solid was suspended in ethanol and a

solution of 0.5 M HCl in ethanol (1.6 mL, 2.5 eq.) was added. The resulting solution was filtered, concentrated, and treated with diethyl ether. The resulting solid was filtered, dried, providing the final title compound(97 mg, 38%). MS (ES+) 345.

Anal. Calcd for $C_{17}H_{17}N_4SCl \cdot HCl \cdot 0.1$ EtOH
Theory: C, 53.53, H, 4.86, N, 14.52.
Found: C, 53.29, H, 4.73, N, 14.21.

Example 115

Preparation of 2-Cyano-4-[2-(2-chlorophenyl)ethylamino] pyrido(2,3-d) pyrimidine hydrochloride.



2,4-Dichloropyrido (2,3-d) pyrimidine.

The intermediate title compound was prepared essentially by the method outlined in *JACS*, 77, 2256 (1955).

2-Chloro-4-[2-(2-chlorophenyl)ethylamino] pyrido(2,3-d) pyrimidine.

A mixture of 2,4-dichloropyrido (2,3-d) pyrimidine (300 mg, 1.50 mmol), 2-(2-chlorophenyl)ethylamine (300 mg, 1.90 mmol), potassium carbonate (415 mg, 3.00 mmol), and 1-methyl-2-pyrrolidinone (5 mL) was heated and stirred at 95-100°C for 1.5 h. The mixture was cooled, poured into a separatory funnel and partitioned between ethyl acetate (30 mL) and brine (30 mL). An insoluble portion was filtered from the biphasic mixture, was filtered, and held aside. The organic layer was backwashed with brine (30 mL), dried over sodium sulfate, and concentrated to a solid. The

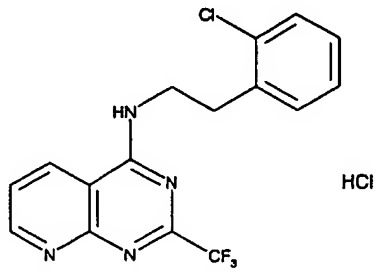
insoluble material obtained earlier was combined with this material and the combined solids were treated with 1:1 diethyl ether / hexanes (50 mL). The resulting tan solid was filtered, suspended in ethanol, and celite (400 mg) was added. The mixture was concentrated to a powder, added to a silica gel column, and eluted with ethyl acetate followed by 2% methanol in methylene chloride. The intermediate title compound was isolated as a pale yellow solid, 380 mg (79%). MS (ES+) 319.

A mixture of 2-chloro-4-[2-(2-chlorophenyl)ethylamino] pyrido(2,3-d) pyrimidine (375 mg, 1.18 mmol), potassium cyanide (765 mg, 11.8 mmol), and dimethylsulfoxide (5 mL) was stirred and heated at 115-120°C for 6 h. The dark solution was poured into a separatory funnel and partitioned between water (50 mL) and 10% isopropanol in chloroform (2 X 50 mL). The combined organics were dried over sodium sulfate and concentrated to an oil. Chromatography over flash silica gel (ethyl acetate) gave a yellow solid of the free base of the final title compound (34 mg). The solid was suspended in ethanol, treated with 0.6 mL (2.5 eq.) of 0.5 M HCl in ethanol, and solution was obtained. The solution was filtered, concentrated, and diethyl ether was added. The resulting solid was filtered and dried to give final title compound (28 mg, 7%). MS (ES+) 310.

Anal. Calcd for $C_{16}H_{12}N_5Cl \cdot HCl \cdot 0.4EtOH$
Theory: C, 55.20, H, 3.90, N, 18.92.
Found: C, 55.33, H, 4.26, N, 19.21.

Example 116

Preparation of 2-trifluoromethyl-4-[2-(2-chlorophenyl)ethylamino]pyrido(2,3-d) pyrimidine hydrochloride.



2-Trifluoromethyl-4-hydroxypyrido(2,3-d) pyrimidine.

A mixture of 2-aminonicotinic acid (2.5 g, 18.1 mmol), 2,2,2-trifluoroacetamide (6.2 g, 54.8 mmol), and 1-methyl-2-pyrrolidinone (30 mL) was refluxed for 18 h. The mixture was cooled and added as such to a flash 65M silica gel cartridge, eluting with 2% methanol in methylene chloride gradually increasing to 5% methanol in methylene chloride. The crude desired was obtained containing 1-methyl-2-pyrrolidinone. The liquid was partitioned between ethyl acetate (100 mL) and water (3 X 100 mL). The organic layer was dried over sodium sulfate and concentrated to a solid which was suspended in ethyl acetate/hexanes, filtered, and dried to give the intermediate title compound (285 mg). The aqueous layer obtained above was extracted in 100 mL portions with ethyl acetate (100 mL). The organic layer was dried over sodium sulfate, concentrated, and treated with methylene chloride/hexanes. After seeding with intermediate title compound obtained above, a second crop of crystals was obtained, 120 mg. The two solids were combined to give the intermediate title compound (405 mg, 10%). MS (ES+) 215.

2-Trifluoromethyl-4-chloropyrido(2,3-d) pyrimidine.

A suspension of 2-trifluoromethyl-4-hydroxypyrido(2,3-d) pyrimidine (404 mg, 1.88 mmol) and phosphorus oxychloride (10 mL) was heated at reflux for 2 h. The solution was cooled, concentrated, and dissolved in chloroform (25 mL).

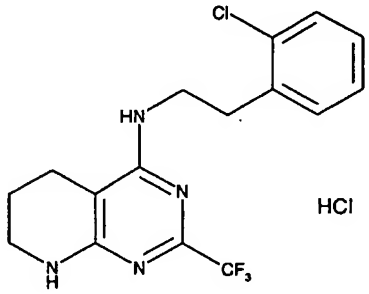
The solution was added to an ice cold stirring solution of aqueous saturated sodium bicarbonate (25 mL), brought to room temperature, and the layers were separated. The organic layer was dried over sodium sulfate, concentrated and chromatographed (flash 40S, 7 X 4 cm cartridge with 40 g silica gel from Biotage, a division of Dyax, 1500 Avon Street, Charlottesville, Virginia 22902, 3:2 hexanes/ethyl acetate) to give a light yellow solid of the intermediate title compound (316 mg, 72%). MS FD+ 233.

Anal. Calcd for $C_8H_3N_3F_3Cl$
Theory: C, 41.14, H, 1.29, N, 17.99.
Found: C, 40.95, H, 1.14, N, 17.74.

A mixture of 2-trifluoromethyl-4-chloropyrido(2,3-d) pyrimidine (300 mg, 1.28 mmol), 2-(2-chlorophenyl)ethylamine (250 mg, 1.61 mmol), and potassium carbonate (355 mg, 2.57 mmol) was heated in 1-methyl-2-pyrrolidinone (7 mL) at 110-120°C for 1.5 h. The reaction mixture was cooled, poured into a separatory funnel, and partitioned with ethyl acetate (25 mL) and brine (2 X 25 mL). An insoluble precipitate was filtered from the initial biphasic mixture and held aside. The organic layer was dried over sodium sulfate and concentrated to a solid which was combined with the precipitated solid earlier obtained. The combined solids were suspended in methylene chloride and filtered. The solid thus obtained was homogeneous desired. The filtrate contained more product and was chromatographed (flash 40S, 4:1 ethyl acetate/hexanes) to provide additional material. The two solids thus obtained were pooled and dried to give the free base of the final title compound (380 mg, 84%). 175 mg (0.5 mmol) of the above solid was dissolved in ethanol, treated with 1.5 mL (3 eq.) of 1M HCl in ethanol, filtered, and concentrated to dryness. Addition of diethyl ether provided the final title compound (176 mg). MS (ES+) 353.

Example 117

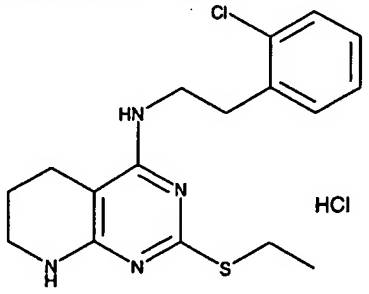
Preparation of 2-trifluoromethyl-4-[2-(2-chlorophenyl)ethylamino]-5:6:7:8-tetrahydro-1:3:8-triazanaphthalene.



A mixture of 2-trifluoromethyl-4-[2-(2-chlorophenyl)ethylamino]pyrido(2,3-d) pyrimidine (200 mg, 0.57 mmol, example 116) and platinum oxide (14 mg) in ethanol (14 mL) was hydrogenated at 60 psi for 1.5 h at room temp. The solution was concentrated to give a solid which was dissolved in ethanol and treated with 1.5 mL (3 eq.) of 1 M HCl in ethanol. The solution was concentrated to dryness, diethyl ether was added, and the resulting solid was filtered and dried to give the title compound (168 mg, 75%). MS (ES+) 357.

Example 118

Preparation of 2-mercaptoethyl-4-[2-(2-chlorophenyl)ethylamino]- 5:6:7:8-tetrahdro-1:3:8-triazanaphthalene hydrochloride.



2-Chloro-4-[2-(2-chlorophenyl)ethylamino]- 5:6:7:8-tetrahydro-1:3:8-triazanaphthalene.

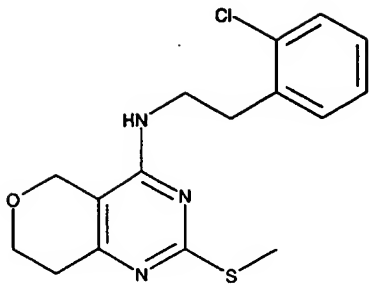
A solution of 2-chloro-4-[2-(2-chlorophenyl)ethylamino]pyrido(2,3-d) pyrimidine (370 mg, 1.16 mmol, example 115) in ethanol (20 mL) containing platinum oxide (30 mg) was hydrogenated at 60 psi, room temperature, for 1 h. The solvent was removed to give a solid which was chromatographed (flash 40S, 2% methanol in methylene chloride) to provide a white solid of intermediate title compound(282 mg, 75%). MS (ES+) 323.

A mixture of 2-chloro-4-[2-(2-chlorophenyl)ethylamino]-5:6:7:8- tetrahydro-1:3:8-triazanaphthalene (50 mg, 0.155 mmol), cupric oxide (6 mg), cupric sulfate pentahydrate (6 mg), ethanethiol (1 mL), and 1-methyl-2-pyrrolidinone (2 mL) was heated and stirred in a pressure tube at 195-200°C for 6 h. The reaction mixture was cooled to room temperature, and the contents were then partitioned between ethyl acetate (20 mL) and brine (2 X 20 mL). The organic layer was dried over sodium sulfate and concentrated to a foam. Chromatography (flash 40S, 0.5% methanol in methylene chloride) gave the free base of the final title compound (35 mg). The solid was suspended in ethanol and 0.4 mL of 0.5 M HCl in ethanol was added. The resulting solution was filtered, concentrated, and dried to give the final title compound (28 mg, 47%). MS (ES+) 349.

Anal. Calcd for $C_{17}H_{21}N_4SCl \cdot HCl \cdot 0.25\ H_2O$
Theory: C, 52.37, H, 5.77, N, 14.37.
Found: C, 52.40, H, 5.64, N, 14.17.

Example 119

Preparation of [2-(2-chlorophenyl)ethyl](2-methylthio(7,8-dihydro-5H-pyrano[3,4-e]pyrimidin-4-yl))amine.



Methyl 4-oxo-2H-3,5,6-trihydropyran-3-carboxylate.

Methyl magnesium carbonate (2.5M in DMF, 13 mL, 32.5mmol) was added to a 100mL round bottom flask containing tetrahydro-4H-pyran-4-one (1 mL, 10.8 mmol) and heated at 110°C while a stream of nitrogen was blown over the mixture. After 30 min, 50 mL diethyl ether was added and the stirred vigorously for 30 min. The solids were then filtered and washed with thoroughly with diethyl ether. The solids were suspended in 100 mL ethyl acetate and added in one portion to an ice-cold solution of 5N HCl (100 mL) After 15 min the mixture was warmed to RT, partitioned, dried with Magnesium sulfate and concentrated to a white solid. The solids were dissolved in 4:1 diethyl ether/methanol (15mL), cooled to 0°C and charged with 10 mL TMS-diazomethane dropwise over 15 min. The reaction mixture was warmed to RT, concentrated and purified on a Flash 40M cartridge, (a 10 X 4 cm cartridge with 00 g silica gel from Biotage, a division of Dyax, 1500 Avon Street, Charlottesville, Virginia 22902), using 15% EtOAc/Hex to provide the intermediate title compound. ^{1}HNMR (400MHz, $CDCl_3$): 2.24 (m, 2H), 3.60 and 3.62 (2s, 3H), 3.70 (t, 2H), 3.85 (m, 0.5H, enol form), 4.12 (t, 2H), 11.6 (s, 0.5H, enol form). MS (ES+): 159.

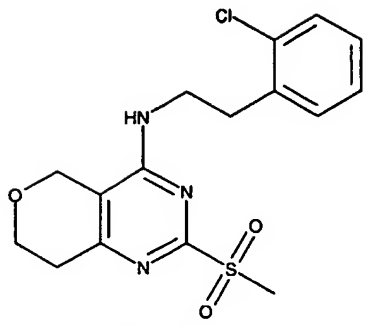
4-Chloro-2-methylthio-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine.

Methyl 4-oxo-2H-3,5,6-trihydropyran-3-carboxylate (177 mg, 1.1 mmol) and S-methyl isothiourea sulfate (156 mg, 0.56 mmol) were added to a suspension of Na_2CO_3 (1.2g, 11 mmol)) in 5mL MeOH at RT for 4 hrs. The solids were filtered, the filtrate was concentrated and the residue was dissolved in water (20 mL.) The pH of the aqueous layer was adjusted to 5 with glacial acetic acid, and extracted into dichloromethane, dried with Magnesium sulfate, and concentrated *in vacuo* to a colorless oil, which solidified upon standing at RT. The solids from above were dissolved in $POCl_3$ (10mL) and heated at 110 °C for one hour. The reaction mixture was concentrated *in vacuo*, redissolved in EtOAc and added dropwise to an ice cold solution of saturated $NaHCO_3$, partitioned, dried with Magnesium sulfate and purified on a Flash 40S cartridge using 10% EtOAc/hex to give the intermediate title compound (135 mg, 57%, over two steps.) ^1H NMR (400MHz, $CDCl_3$): 2.49 (s, 3H), 2.84 (t, 2H), 3.95 (t, 2H). MS (ES+):217.

4-Chloro-2-methylthio-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (130mg, 0.6mmol) was dissolved in 5 mL NMP, followed by 2(2-chlorophenyl)ethylamine (84µl, 0.6mmol) and pyridine (121 µL, 1.5 mmol). Stirred at 100°C for 90 min. Diluted with EtOAc, washed with brine (2x), dried with Magnesium sulfate, concentrated and purified on a Flash 40S cartridge (20% EtOAc/Hex) to give 81 mg (40%) of final title compound. ^1H NMR (400MHz, $CDCl_3$): 2.50 (s, 3H), 2.70 (t, 2H), 3.03 (t, 2H), 3.75 (q, 2H), 3.90 (t, 2H), 4.30 (s, 2H), 7.15 (m, 3H), 7.33 (m, 1H). MS (ES+): 336.

Example 120

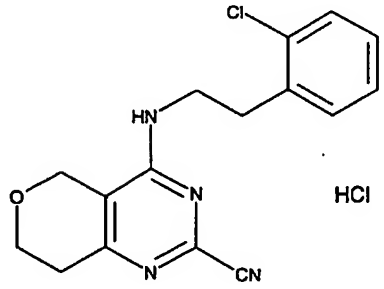
Preparation of 4-{[2-(2-chlorophenyl)ethyl]amino}-2-(methylsulfonyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine.



4-Chloro-2-methylthio-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (114 mg, 0.53 mmol, example 119) was dissolved in dichloromethane (5 mL) and charged with MCPBA (50% w/w, 365 mg, 1.1mM) and stirred at RT. After 3 hrs the reaction mixture consisted mostly of sulfoxide, as determined by MS. MCPBA was added again in 10mg portions in 30-min intervals until only sulfone was observed by MS (a total of 60mg). Partitioned reaction mixture with saturated $NaHCO_3$ solution, dried organics with Magnesium sulfate, concentrated *in vacuo* and purified on a Flash 40S cartridge (40% EtOAc/Hex) to give 106 mg (80%) of title compound. ^{1}HNMR (400 MHz, $CDCl_3$): 3.07 (t, 2H), 3.30 (s, 3H), 4.04 (t, 2H), 4.75 (s, 2H). MS (ES+) 249.

Example 121

Preparation of 4-{[2-(2-chlorophenyl)ethyl]amino}-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine-2-carbonitrile hydrochloride.

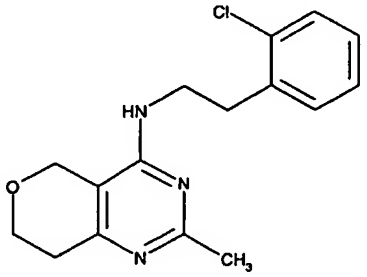


4-{[2-(2-Chlorophenyl)ethyl]amino}-2-(methylsulfonyl)-7,8-dihydro-5H-pyrano[4,3-d]pyrimidine (90 mg, 0.36 mmol, example 120) was dissolved in NMP and charged with 2(2-chlorophenyl)ethylamine (51 µL, 0.36 mmol) and pyridine (58

μL, 0.72mmol) and stirred at 100°C for 4 hrs. Solid KCN (470mg, 7.2 mmol) was added to the reaction mixture and stirred at 100°C for 24 hrs. The reaction mixture was diluted with EtOAc, washed with brine (2x), dried with Magnesium sulfate, concentrated and purified on a Flash 40S cartridge (30% EtOAC/Hex). The appropriate fractions were concentrated and charged with 2 mL 0.5M ethanolic HCl and 1 mL methanol to aid solubilization. After one hour at RT the mixture was concentrated and triturated with diethyl ether. The resulting solids were filtered and dried under high vacuum at 60°C overnight to give 44mg (35%) of the title compound. ^{1}H NMR (400MHz, DMSO): 2.65 (t, 2H), 2.95 ((t, 2H), 3.59 (q, 2H), 3.85 (t, 2H), 4.40 (s, 2H), 7.25-7.56 (m, 4H). MS (ES+) 314.

Example 122

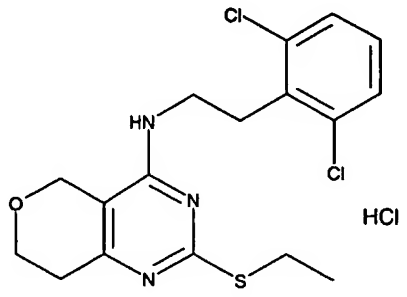
Preparation of [2-(2-chlorophenyl)ethyl](2-methyl(7,8-dihydro-5H-pyrano[3,4-e]pyrimidin-4-yl))amine.



The title compound was synthesized in the same fashion as the procedure set forth in example 121, except acetamidine HCl was used instead of S-methyl isothiourea sulfate. ^{1}H NMR (400MHz, DMSO-d_6): 2.41 (s, 3H), 2.69 (t, 2H), 2.94 (t, 2H), 3.67 (t, 2H), 3.84 (t, 2H), 4.34 (s, 2H), 7.17-7.38 (m, 4H). MS (ES+)305.

Example 123

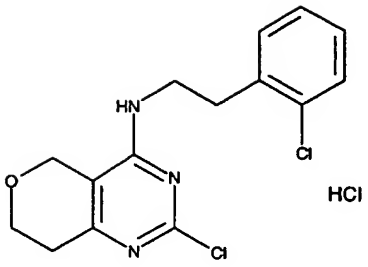
Preparation of [2-(2,6-dichlorophenyl)ethyl](2-ethylthio(7,8-dihydro-5H-pyrano[3,4-e]pyrimidin-4-yl))amine hydrochloride.



The title compound was synthesized in the same manner as the procedure set forth in example 120, except in the synthesis of its precursor, as described in example 119, instead of S-methyl isothiourea sulfate, 2-ethyl-2-thiopseudo urea HBr was used, and in the synthesis of the precursor following the procedure in example 120, instead of 2(2-chlorophenyl)ethylamine, 2,6-dichlorophenethyl amine was used. After purification the obtained solids were treated with 0.5M ethanolic HCl , allowed to stand at RT for one hour, concentrated to low volume and triturated with diethyl ether to obtain 52 mg of a white solid which was dried under high vacuum at 60°C to provide the title compound. ^{1}H NMR (400MHz, DMSO-d6): 1.4 (t, 3H), 2.52 (t, 2H), 3.15 (m, 4H), 3.54 (m, 4H), 4.35 (s, 2H), 7.22 (t, 1H), 7.39 (d, 2H). MS (ES+) 384.

Example 124

Preparation of (2-chloro(7,8-dihydro-5H-pyrano[3,4-e]pyrimidin-4-yl))[2-(2-chlorophenyl)ethyl]amine hydrochloride.



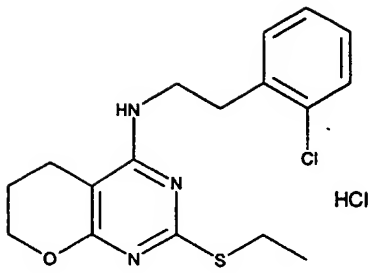
4-{[2-(2-chlorophenyl)ethyl]amino}-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-ol.

[2-(2-Chlorophenyl)ethyl](2-methylthio(7,8-dihydro-5H-pyrano[3,4-e]pyrimidin-4-yl))amine (42 mg, 0.13 mmol, example 119) was dissolved in glacial acetic acid (1mL) and charged with H_2O_2 (30%, 57 µl, 0.5 mmol) and heated at reflux for one hour. The mixture was concentrated, diluted with EtOAc and washed with saturated $NaHCO_3$, dried with Magnesium sulfate and concentrated *in vacuo*. This material was taken the to next step without further purification.

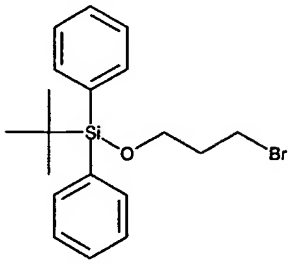
4-{[2-(2-Chlorophenyl)ethyl]amino}-7,8-dihydro-5H-pyrano[4,3-d]pyrimidin-2-ol was dissolved in $POCl_3$ and heated at 110°C for 4 hrs. Concentrated *in vacuo*, redissolved in EtOAc and added dropwise to an ice-cold solution of saturated $NaHCO_3$. The layers were separated and the organics dried with Magnesium sulfate. The residue was treated with 0.5M ethanolic HCl, allowed to stand at RT for one hour, concentrated and triturated with dichloromethane and placed in the freezer overnight. Filtered solids to give the final title compound (4.1mg, 87%) as a light tan solid. ^{1}HNMR (400MHz, DMSO-d_6, 1 drop D_2O): 2.52 (t, 2H), 2.88 (t, 2H), 3.49 (t, 2H), 3.77 (t, 2H), 4.25 (s, 2H), 7.18-7.39 (m, 4H). MS (ES+): 238.

Example 125

Preparation of [2-(2-chlorophenyl)ethyl](2-ethylthio(6,7-dihydro-5H-pyrano[3,2-e]pyrimidin-4-yl))amine hydrochloride.



1-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-3-bromopropane.



3-bromo propanol (5 mL, 55 mmol), t-butylchlorodiphenyl silane (21.5 mL, 83mmol), triethylamine (15 mL, 110mmol), and DMAP (100 mg) were dissolved in 200mL dichloromethane and stirred at RT for 18 hrs. The mixture was then diluted and washed with brine and water, dried with Magnesium sulfate and concentrated in vacuo. Purified on a Flash 65M cartridge (1%EtOAc/Hexanes) to give 12.5g (60%) of intermediate title compound. ^{1}H NMR (400MHZ, $CDCl_3$): 1.01 (s, 9H), 2.03 (m, 2H), 3.55 (t, 2H), 3.74 (t, 2H), 7.39 (m,6H), 7.61 (m, 4H).

Ethyl phenylmethyl 2-[3-(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)propyl]propane-1,3-dioate.

Benzylethylmalonate, tetrabutylammonium iodide and Cs_2CO_3 were azeotroped from toluene and dried under high vacuum prior to use. 1-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)-3-bromopropane (315 mg, 0.83mmol) was added to a dry 5mL round bottom flask, equipped with a reflux condenser, containing benzylethylmalonate (185 µL, 0.83 mmol), Cs_2CO_3 (406 mg, 1.25mmol) and tetrabutylammonium iodide (10mg) in anhydrous THF (2mL) and heated at reflux for 18 hrs. The

reaction mixture was then cooled to RT, the solids were filtered and the filtrate concentrated. The residue was purified on a Flash 40M cartridge (10% EtOAc/Hexanes) to give 370mg (86%) of the intermediate title compound. ^{1}H NMR (400MHz,$CDCl_3$): 0.96 (s, 9H), 1.12 (t, 3H), 1.49 (m, 2H), 1.95 (m, 2H), 3.34 (t, 1H), 3.58 (t, 2H), 4.09 (q, 2H), 5.09 (s, 2H), 7.2-7.4 (m, 11H), 7.56 (dd, 4H).

5-[3-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)propyl]-2-ethylthiopyrimidine-4,6-diol.

Ethyl phenylmethyl 2-[3-(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)propyl]propane-1,3-dioate (7.67g, 14.8 mmol) was added to a suspension of 10% Pd/C in ethanol and stirred under a H_2 atmosphere for 90 minutes. The catalyst was then filtered, washed with ethanol and the filtrate was concentrated *in vacuo* and placed under high vacuum overnight. The free acid (6.3g, 14.7mmol) was dissolved in anhydrous DMF and charged with EDCI (4.23g, 22.1mmol) and N-hydroxysuccinimide (2.53 g, 22.1mmol) and stirred at RT for 3 hrs. 2-ethyl-2-thiopseudourea HBr (4.1g, 22.1mmol) and Hunig's base (7.7 mL, 44.2mmol) were added and the mixture was stirred at RT for 20 hrs to give a mixture of ethyl 5-(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)-2-[N-(ethylthioiminomethyl)carbamoyl]pentanoate and 5-[3-(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)propyl]-2-ethylthiopyrimidine-4,6-diol within a fairly complex reaction mixture. Purified on a Flash 65M cartridge using 1L each 10%, 20%, and 30% EtOAc/Hexanes). Ethyl 5-(2,2-dimethyl-1,1-diphenyl-1-silapropoxy)-2-[N-(ethylthioiminomethyl)carbamoyl]pentanoate was then dissolved in toluene and heated at 120°C for 24 hrs. This mixture was then cooled in a freezer for 6 hrs, the solids were filtered to give a total of 920mg (16%) of intermediate title compound. ^{1}H NMR(400MHz, DMSO-d6) 0.99 (s, 9H), 1.29

(t, 3H), 1.69 (t, 2H), 2.31 (bt, 2H), 3.10 (q, 2H), 3.64 (t, 2H), 7.44 (m, 6H), 7.63 (m, 4H).

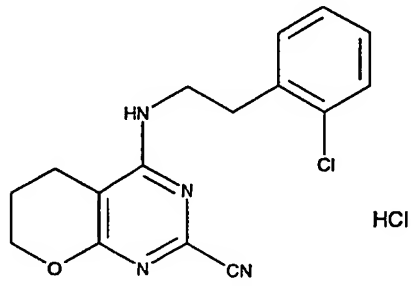
4-Chloro-2-ethylthio-6,7-dihydro-5H-pyrano[2,3-d]pyrimidine hydrochloride.

5-[3-(2,2-Dimethyl-1,1-diphenyl-1-silapropoxy)propyl]-2-ethylthiopyrimidine-4,6-diol (752 mg, 1.6 mmol) was suspended in POCl3 (15mL) and heated until a homogenous solution was obtained (ca. 45 min), the mixture was then cooled to RT, concentrated in vacuo, redissolved in EtOAc, and added slowly to an ice-cold solution of saturated NaHCO3. The layers were then separated, the organics dried with Magnesium sulfate and concentrated in vacuo. Purified on a Flash 40M cartridge (20% EtOAc/Hexanes) to give 320mg (86%) of intermediate title compound. ^{1}H NMR (400MHz, CDCl3): 1.47 (t, 3H), 2.1 (m, 2H), 2.75 (t, 2H), 3.14 (q, 2H), 4.40 (t, 2H). MS (ES+): 231.

4-Chloro-2-ethylthio-6,7-dihydro-5H-pyrano[2,3-d]pyrimidine hydrochloride (445 mg, 1.9 mmol), 2(2-chlorophenyl)ethylamine (408 µL,2.9 mmol), and Hunig's base (827 µL, 4.8 mmol) were dissolved in NMP and stirred at 90°C overnight. The reaction mixture was then diluted with EtOAc and washed with brine and water. Purified on a Flash 40M cartridge (30% EtOAc/Hexanes). The pooled fractions were concentrated and treated with 10mL 0.5M ethanolic HCl, allowed to stand at RT for one hour, concentrated to low volume and treated with diethyl ether to produce white solids. These were filtered and dried under high vacuum at 60°C to give 520 mg (71%) of the final title compound. ^{1}H NMR (400MHz, CDCl3): 1.32 (t, 3H), 1.58 (bt, 2H), 2.28 (t, 2H), 3.00 (m, 4H), 3.15 (bs, 2H), 4.25 (t, 2H)7.24-7.45 (m, 4H). MS (ES+): 350.

Example 126

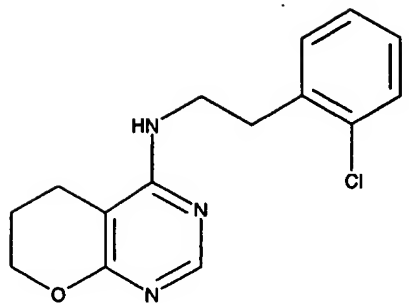
Preparation of 4-{[2-(2-chlorophenyl)ethyl]amino}-6,7-dihydro-5H-pyrano[2,3-d]pyrimidine-2-carbonitrile hydrochloride.



[2-(2-Chlorophenyl)ethyl](2-ethylthio(6,7-dihydro-5H-pyrano[3,2-e]pyrimidin-4-yl))amine (414 mg, 1.2 mmol, example 125) was dissolved in dichloromethane (5mL) and treated with MCPBA (70% w/w, 590 mg, 2.4 mmol) and stirred at RT for 2 hrs. Diluted reaction with dichloromethane and added 20mL saturated $NaHCO_3$ and stirred vigorously for 30 min. The organic layer was dried with Magnesium sulfate, and concentrated *in vacuo* to a colorless oil. This oil was then dissolved in DMSO (5mL) and treated with KCN (781 mg, 12 mmol) and stirred at 100°C overnight. Diluted with EtOAc, washed with brine and water, dried with Magnesium sulfate and purified on a Flash 40M cartridge (30% EtOAc/Hexanes). The pooled fractions were concentrated and treated with 10mL 0.5M ethanolic HCl, allowed to stand at RT for one hour, concentrated to low volume and treated with diethyl ether to produce white solids. These were filtered and dried under high vacuum at 60°C to give 252 mg (60%) of title compound. ^1H NMR (400MHz, DMSO-d_6): 1.9 (t, 2H), 2.4 (t, 2H), 3.0 (t, 2H), 3.65 (q, 2H), 4.24 (t, 2H), 7.20-7.45 (m, 4H). MS (ES+): 315.

Example 127

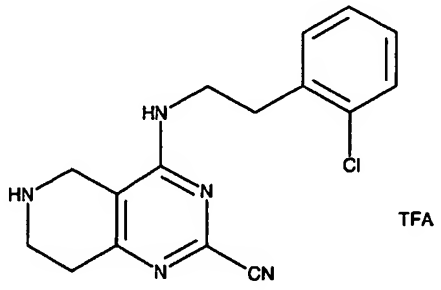
Preparation of [2-(2-chlorophenyl)ethyl]-6,7-dihydro-5H-pyrano[3,2-e]pyrimidin-4-ylamine.



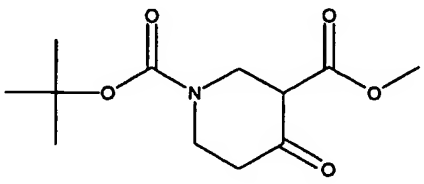
[2-(2-Chlorophenyl)ethyl](2-ethylthio(6,7-dihydro-5H-pyrano[3,2-e]pyrimidin-4-yl))amine hydrochloride (530 mg, 1.4 mmol, example 125) was added to a suspension of Rainey® Nickel (2g) in ethanol and agitated on a Parr shaker for 30 hrs. After filtration of the catalyst the solvent was evaporated to give 224 mg (52%) of the title compound in excellent purity. ^{1}H NMR (400MHz, DMSO-d6): 1.88 (t, 3H), 2.27 (t, 3H),2.95 (t, 3H), 3.57 (q, 2H), 4.18 (t, 3H), 6.74 (t, 1H, NH), 7.20-7.41 (m, 4H), 7.99 (s, 1H). MS (ES+): 290.

Example 128

Preparation of 4-{[2-(2-chlorophenyl)ethyl]amino}-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-2-carbonitrile trifluoroacetate.



Methyl 1-[(tert-butyl)oxycarbonyl]-4-oxopiperidine-3-carboxylate.



BOC-anhydride (16.9 g, 77.4 mmol) was added to a solution of methyl 4-oxo-3-piperidine-carboxylate hydrochloride (10 g, 51.6 mmol) and triethylamine (14 mL, 103 mmol) in dichloromethane (100mL) and stirred at RT overnight. Concentrated to low volume, filtered solids and purified on a Flash 65M cartridge (10% EtOAc/Hexanes) to give 13.1g (98%) intermediate title compound. ^{1}H NMR (400MHz. CDCl3): 1.47 (s, 9H), 2.36 (bt, 2H), 3.54 (t, 2H), 3.77 (s, 3H), 4.04 (s, 2H).

tert-Butyl 2-ethylthio-4-[(trifluoromethyl)sulfonyloxy]-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-6-carboxylate.

Methyl 1-[(tert-butyl)oxycarbonyl]-4-oxopiperidine-3-carboxylate (1.0g, 3.9 mmol) was dissolved in 1:1 Dioxane/water (10mL) and treated with 2-ethyl-2-thiopseudo urea HBr (791 mg, 4.3 mmol) and sodium carbonate (1.24 g, 11.7 mmol) and stirred at RT for 24 hrs. The mixture was treated with glacial acetic acid until the pH reached 5 and then extracted with 10% isopropyl alcohol/Chloroform, dried with Magnesium sulfate and concentrated *in vacuo* to white solids (1g). The crude solids were subsequently dissolved in dichloromethane, treated with pyridine (650 µL, 8.0 mmol) and cooled to -40°C. Trifluoromethane sulfonic anhydride (810 µL, 4.8 mmol) was added dropwise. The dark brown reaction mixture was stirred at -40°C for 30 min, then warmed to RT, diluted with dichloromethane, washed with brine, dried with Magnesium sulfate, and concentrated. Purified on a Flash 40L cartridge (21 X 4 cm cartridge with 120 g silica gel from Biotage, a division of Dyax, 1500 Avon Street, Charlottesville, Virginia 22902, 10%EtOAc/Hexanes) to give 904 mg (52%) of the intermediate title compound. ^{1}H NMR (400MHz, CDCl3): 1.34 (t, 3H), 1.44 (s, 9H), 2.88 (t, 2H), 3.06 (q, 2H), 3.70 (t, 2H), 4.46 (s, 2H). MS (ES+): 444.

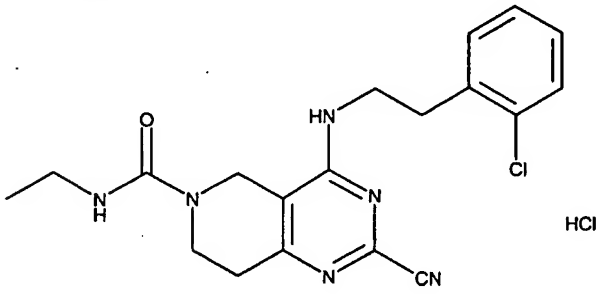
tert-Butyl 4-{[2-(2-chlorophenyl)ethyl]amino}-2-cyano-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-6-carboxylate.

tert-Butyl 2-ethylthio-4-[(trifluoromethyl)sulfonyloxy]-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-6-carboxylate (900 mg, 2.1 mmol) was dissolved in dichloromethane. Added MCPBA (70%w/w, 1.0g, 4.2 mmol) and stirred at RT for one hour. The mixture was diluted with dichloromethane and washed with brine and water, partitioned and purified on a Flash 40M cartridge to give 876 mg (88%) of the sulfone. The sulfone was dissolved in NMP, added 2-(2-chlorophenyl) ethylamine (311 µL, 2.2 mmol) and Hunig's base (383 µL, 2.2 mmol) and stirred at RT for 30 min. The mixture was warmed to 100°C, added KCN (586 mg, 9.0 mmol) and stirred at that temperature for18 hrs. The mixture was cooled to RT, diluted with EtOAc, washed with brine and dried with Magnesium sulfate. Purified on a Flash 40L cartridge (25% EtOAc/Hexanes) to give 280 mg (38%) of the intermediate title compound. ^{1}H NMR (400MHz, CDCl3): 1.42 (s, 9H), 2.74 (t, 2H), 3.02 (bs, 2H), 3.62 (t, 2H), 3.75 (t, 2H), 4.10 (s, 2H), 7.12-7.32 (m, 4H). MS (ES+): 414.

tert-Butyl 4-{[2-(2-chlorophenyl)ethyl]amino}-2-cyano-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-6-carboxylate (3.4 g, 8.2 mmol) was treated with trifluoroacetic acid and dichloromethane (15 mL/25mL) and stirred at RT for 3 hrs. Concentrated in vacuo to low volume, added 100 mL diethyl ether, filtered solids and dried under high vacuum at 40°C to give 3.2 g (72%) of final title compound. . ^{1}H NMR (400MHz, DMSO-d6): 2.87 (t, 2H), 3.01 (t, 2H), 3.41 (t, 2H), 3.64 (q, 2H), 3.98 (s, 2H), 7.24-7.41 (m, 4H), 7.87 (t, 1H, NH).

Example 129

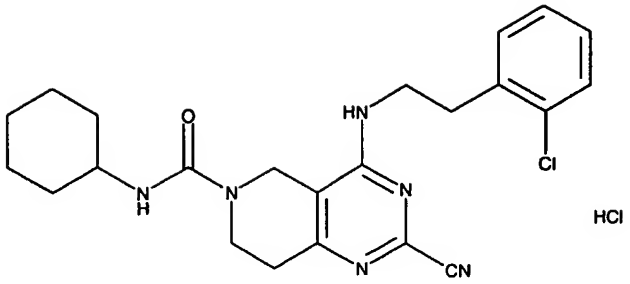
Preparation of (4-{[2-(2-chlorophenyl)ethyl]amino}-2-cyano(5,6,7,8-tetrahydropyridino[4,3-d]pyrimidin-6-yl))-N-ethylcarboxamide hydrochloride.



To a suspension of 4-{[2-(2-chlorophenyl)ethyl]amino}-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-2-carbonitrile trifluoroacetate(143 mg, 0.26mmol, example 128, free based *in situ* with either Hunig's base or pyridine) in dichloromethane was added ethylisocyanate (25 µL, 0.32 mmol) and Hunig's base (135 µL, 0.78 mmol) and the mixture was stirred at RT for 3 hrs. The reaction mixture was applied directly to a Flash 40s cartridge and purified using 3:1 EtOAc/Hexanes. The resulting urea was treated with 0.5M ethanolic HCl, allowed to stand at RT for 2 hrs, concentrated and triturated with diethyl ether to give 93mg (85%) of the final title compound. ^{1}H NMR(400MHz, DMSO-d6): 1.05 (t, 3H), 2.78 (t, 2H), 3.04 (m, 4H), 3.62 (m, 4H), 4.21 (2H), 7.25-7.43 (m, 4H), 7.63 (t, 1H, NH). MS (ES+) 385.

Example 130

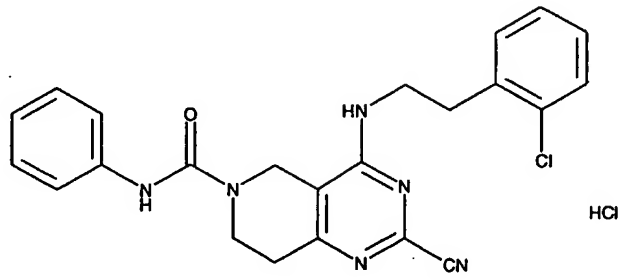
Preparation of (4-{[2-(2-chlorophenyl)ethyl]amino}-2-cyano(5,6,7,8-tetrahydropyridino[4,3-d]pyrimidin-6-yl))-N-cyclohexylcarboxamide hydrochloride.



The title compound was prepared in a manner analogous to the procedure described in example 129. ^{1}H NMR (400MHz, DMSO): 1.0-1.25 (m, 6H), 1.4-1.8 (m, 6H), 2.57 (t, 2H), 2.94 (t, 2H)3.53 (m, 4H), 4.12 (s, 2H), 7.20-7.24 (m, 4H), 7.35 (dd, 1H, NH), 7.55 (t, 1H, NH). MS (ES+)439.

Example 131

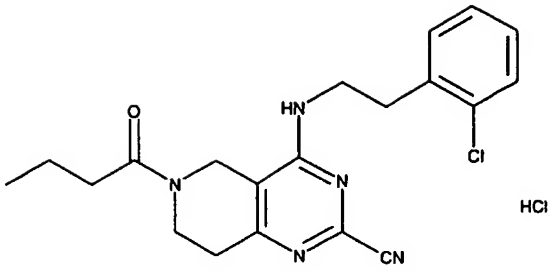
Preparation of (4-{[2-(2-chlorophenyl)ethyl]amino}-2-cyano(5,6,7,8-tetrahydropyridino[4,3-d]pyrimidin-6-yl))-N-benzamide hydrochloride.



The title compound was prepared in a manner analogous to the procedure described in example 129. ^{1}H NMR (400MHz, DMSO) 2.69 (t, 2H), 2.95 (t, 2H), 3.58 (q, 2H), 3.70 (t, 2H), 4.28 (s, 2H), 6.89 (t, 1H), 7.15-7.42 (m, 8H), 7.66 (1H, NH)MS (ES+) 433.

Example 132

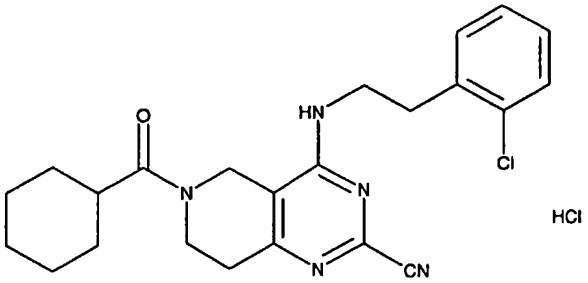
Preparation of 6-butanoyl-4-{[2-(2-chlorophenyl)ethyl]amino}-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-2-carbonitrile hydrochloride.



The title compound was prepared in a manner analogous to the procedure described in example 129. MS: (ES+): 384

Example 133

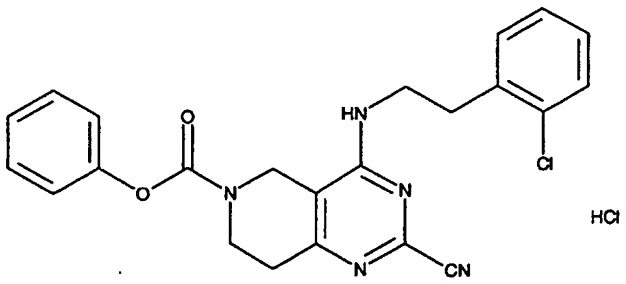
Preparation of 4-{[2-(2-chlorophenyl)ethyl]amino}-6-(cyclohexylcarbonyl)-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-2-carbonitrile hydrochloride.



The title compound was prepared in a manner analogous to the procedure described in example 129. MS (ES+): 424

Example 134

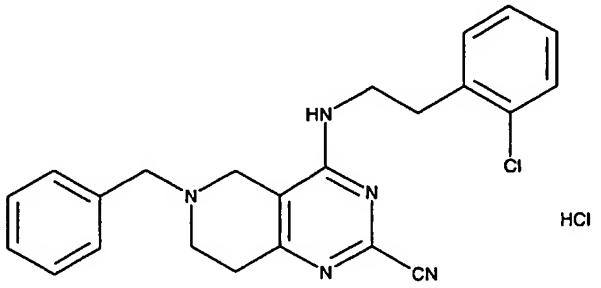
Preparation of phenyl 4-{[2-(2-chlorophenyl)ethyl]amino}-2-cyano-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-6-carboxylate hydrochloride.



The title compound was prepared in a manner analogous to the procedure described in example 129. MS (ES+): 434.

Example 135

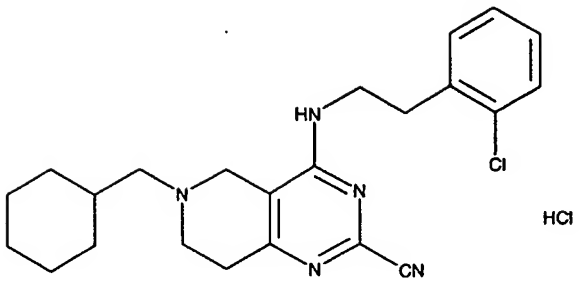
Preparation of4-{[2-(2-chlorophenyl)ethyl]amino}-6-benzyl-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-2-carbonitrile hydrochloride.



4-{[2-(2-Chlorophenyl)ethyl]amino}-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-2-carbonitrile trifluoroacetate (20 mg, 0.037 mmol) and benzaldehyde (7.5 μL, 0.074 mmol) were dissolved and stirred in methanol (1mL) for 30 min. $NaCNBH_3$ (2.5 mg, 0.41 mmol) was added and continued to stir at RT for 30 min. The reaction mixture was concentrated, redissolved in dichloromethane, washed with saturated $NaHCO_3$ solution and dried with Magnesium sulfate. Purified on a Flash 12M cartridge (15% EtOAc/ Hexanes) to give 6.5 mg (40%) of the free base of the title compound. The free base was treated with 0.5M ethanolic HCl (3 equivalents), allowed to stand at RT for two hours and triturated with diethyl ether to produce the product as a solid which was filtered and dried in a 60°C vacuum oven. MS (ES+): 404.

Example 136

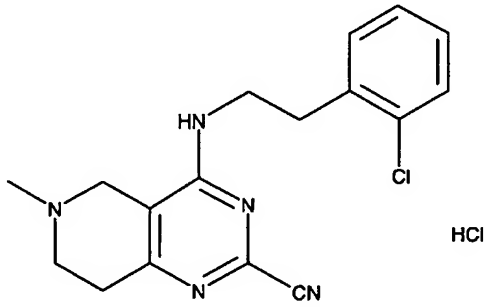
Preparation of 4-{[2-(2-chlorophenyl)ethyl]amino}-6-(cyclohexylmethyl)-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-2-carbonitrile hydrochloride.



The title compound was prepared in a manner analogous to the procedure described in example 135. MS (ES+): 410.

Example 137

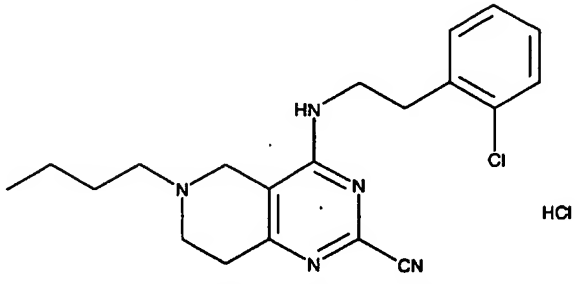
Preparation of 4-{[2-(2-chlorophenyl)ethyl]amino}-6-methyl-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-2-carbonitrile hydrochloride.



The title compound was prepared in a manner analogous to the procedure described in example 135. MS (ES+): 328.

Example 138

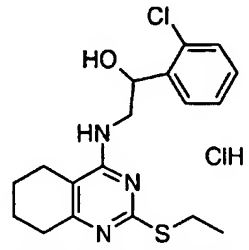
Preparation of 6-butyl-4-{[2-(2-chlorophenyl)ethyl]amino}-5,6,7,8-tetrahydropyridino[4,3-d]pyrimidine-2-carbonitrile hydrochloride.



The title compound was prepared in a manner analogous to the procedure described in example 135. MS (ES+): 370

Example 139

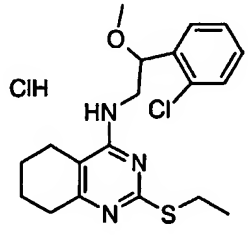
Preparation of N-(2-(2-chlorophenyl)-2-hydroxyethyl)-2-(ethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.



2-amino-1-(2-chlorophenyl)ethanol and 4-chloro-5,6,7,8-tetrahydro-2-ethylthioquinazoline were dissolved in dimethylformamide (10 mL). Diisopropyl ethylamine (300 mg, 2.3 mmol) was added, the mixture was stirred under N_2 and heated at 50°C for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:3) to give a dark oil which was taken up in ethanol (5 mL). 0.5M ethanolic HCl (4 mL) was then added followed by diethyl ether (30 mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 191-193°C.

Example 140

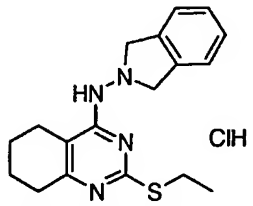
Preparation of N-(2-(2-chlorophenyl)-2-methoxyethyl)-2-(ethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.



Prepared in a similar manner to the above example 139 from 4-chloro-5,6,7,8-tetrahydro-2-ethylthioquinazoline and 2-amino-1-(2-chlorophenyl)-2-methoxyethane, melting point 168-170 °C.

Example 141

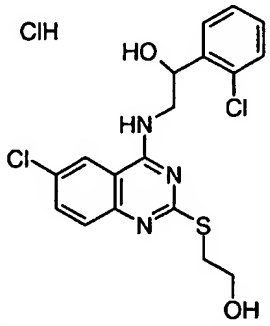
Preparation of N-(1,3-dihydro-2H-isoindol-2-yl)-2-(ethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.



Prepared in a similar manner to the above example 139 from 4-chloro-5,6,7,8-tetrahydro-2-ethylthioquinazoline and 2-aminoisoindoline, melting point 157-159 °C.

Example 142

Preparation of N-(2-(2-chlorophenyl)-2-hydroxyethyl)-2-(2-hydroxyethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.

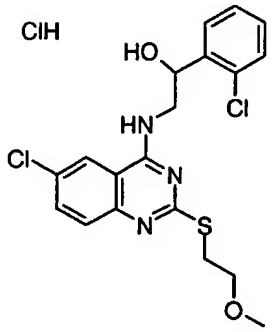


N-(2-(2-chlorophenyl)-2-hydroxyethyl)-2-(ethylthio)-5,6-dimethylpyrimidine-4-amine (0.5g, 1.37 mmol) was dissolved in acetone/water (19:1) (40 mL) and stirred at ambient temperature. Oxone® (1.75g, 2.85 mmol) dissolved in water (10 mL) was added portionwise to the stirred reaction mixture. When addition was complete, the mixture was left to stir at ambient temperature for 18 hours. The mixture was concentrated under reduced pressure and partitioned between ethyl acetate and water. The organic phase was

dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was dissolved in N-methylpyrrolidinone (15 mL) and stirred at ambient temperature under nitrogen. Potassium-*tert*-butoxide (150 mg, 1.3 mmol) was added followed by mercaptoethanol (1 mL). The mixture was stirred and heated under nitrogen at 90°C for 18 hours. The reaction mixture was poured into aqueous ammonium chloride solution (150 mL) and extracted into ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate) to give a clear oil which was taken up in ethanol (5 mL), 0.5M ethanolic HCl (1 mL) was added followed by diethyl ether (70 mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 199-201°C.

Example 143

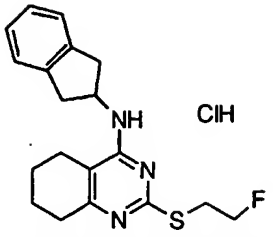
Preparation of N-(2-(2-chlorophenyl)-2-methoxyethyl)-2-(2-hydroxyethylthio)- 5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.



Prepared in a similar manner to the above example 142 from N-(2-(2-chlorophenyl)-2-hydroxyethyl)-2-(ethylthio)-5,6-dimethylpyrimidine-4-amine and 2-methoxy ethanethiol. Melting point 179-181°C.

Example 144

Preparation of N-(2,3-Dihydro-1H-inden-2-ylamino)-2-[(2-fluoroethyl)thio]-5,6,7,8-tetrahydroquinazoline hydrochloride.

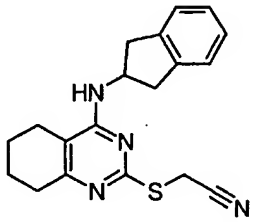


2,3,5,6,7,8-Hexahydro-2-thioxo-4(1H)-quinazolinone (3.15g, 17.3 mmol) was dissolved in dimethylformamide. Potassium *t*-butoxide (1.9g, 17 mmol) was added followed by bromofluoroethane (2.2g, 17.3 mmol) and the reaction mixture was stirred and heated to 45°C under nitrogen for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent chloroform/methanol, 19:1) to give a white solid (3.25g) which was dissolved in dichloroethane(15 mL). Phosphorous oxychloride (10 mL) was added and the reaction mixture was heated to reflux under nitrogen for 18 hours. The reaction mixture was concentrated under reduced pressure, taken up in chloroform and washed with saturated aqueous solution of sodium hydrogen carbonate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. Chromatography on silica gel (eluent ethyl acetate/hexane 1:4) gave 1.9g of yellow oil. A portion of this oil (0.8g) was dissolved in N-methylpyrrolidinone (10 mL), 2-aminoindane (0.43g) and potassium carbonate (0.45g) was added and the reaction mixture was heated at 85°C for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane) to give a dark oil which was taken up in ethanol (5 mL). 0.5M Ethanolic HCl (2 mL) was then added followed by diethyl ether (30 mL). A white solid

crystallized on standing and was collected by filtration to give the title compound, melting point 142-144°C.

Example 145

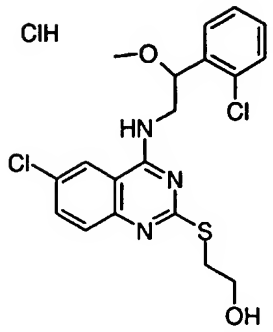
Preparation of {[4-(2,3-dihydro-1H-inden-2-ylamino)-5,6,7,8-tetrahydro-2-quinazolinyl]thio}acetonitrile.



[(1,4-dihydro-4-oxo-2-quinazolinyl)thio]acetonitrile (0.575 g) was dissolved in dichloroethane(15 mL). Phosphorus oxychloride (10 mL) was added and the reaction mixture was heated to reflux under nitrogen for 18 hours. The reaction mixture was concentrated under reduced pressure and washed with saturated aqueous solution of sodium hydrogen carbonate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. Chromatography on silica gel (eluent ethyl acetate/hexane 1:2) gave 0.39 g of dark oil. This oil was dissolved in N-methylpyrrolidinone (10 mL), 2-aminoindane (0.225 g) and potassium carbonate (0.25 g) was added and the reaction mixture was heated at 85°C for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane 1:3) to give a white solid, which was recrystallized from hot ethyl acetate/hexane to give the title compound, melting point 191-193°C.

Example 146

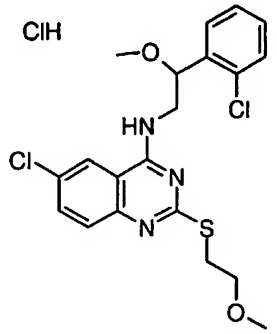
Preparation of 2-[(6-Chloro-4-{[2-(2-chlorophenyl)-2-methoxyethyl]amino}-2-quinazolinyl)thio]ethanol hydrochloride.



2,4,6-Trichloroquinazoline (0.41 g), 2-amino-1-(2-chlorophenyl)-2-methoxyethane (0.325 g) and diisopropylethylamine (0.25 g) were dissolved in dimethylformamide (10 mL) and stirred under nitrogen at ambient temperature for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluent ethyl acetate /hexane, 1:5) to give 0.49g of a yellow solid. 0.36 g of this material was dissolved in N-methylpyrrolidinone (10 mL) and stirred at ambient temperature under nitrogen. Potassium-*tert*-butoxide (165 mg, 2.36 mmol) was added followed by mercaptoethanol (0.5 mL). The mixture was stirred and heated under nitrogen at 85°C for 2 days. The reaction mixture was poured into aqueous ammonium chloride solution (70 mL) and extracted into ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:3) to give white solid. This was taken up in ethanol (5 mL), 0.5M Ethanolic HCl (4 mL) was then added followed by diethyl ether (50 mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 162-164°C.

Example 147

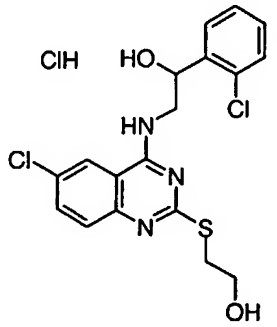
Preparation of 6-Chloro-N-[2-(2-chlorophenyl)-2-methoxyethyl]-2-[(2-methoxyethyl)thio]-4-quinazolineamine hydrochloride.



Prepared in a similar manner to the above example 146 using 2-methoxy ethanethiol in the second part. Melting point 153-155°C.

Example 148

Preparation of 2-[(6-Chloro-4-{[2-(2-chlorophenyl)-2-hydroxyethyl]amino}-2-quinazolinyl)thio]ethanol hydrochloride.

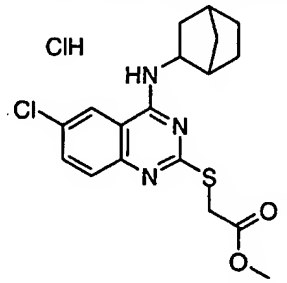


2,4,6-Trichloroquinazoline (1.25 g), 2-amino-1-(2-chlorophenyl)ethanol (1.1 g) and diisopropylethylamine (0.95 g) were dissolved in N-methylpyrrolidinone (10 mL) and stirred under nitrogen and heated to 85°C for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluent ethyl acetate /hexane, 1:3) to give 1.77 g of a yellow solid. 0.5 g of this material was dissolved in N-methylpyrrolidinone (10 mL) and stirred at ambient

temperature under nitrogen. Potassium-*tert*-butoxide (0.24 g, 2.3 mmol) was added followed by mercaptoethanol (0.4 mL). The mixture was stirred and heated under nitrogen at 80°C for 3 days. The reaction mixture was poured into aqueous ammonium chloride solution (70 mL) and extracted into ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:1) to give yellow oil. This was taken up in ethanol (5 mL), 0.5M Ethanolic HCl (3 mL) was then added followed by diethyl ether (50 mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 165-166°C.

Example 149

Preparation of Methyl {[4-(bicyclo[2.2.1]hept-2-ylamino)-6-chloro-2-quinazolinyl]thio}acetate hydrochloride.

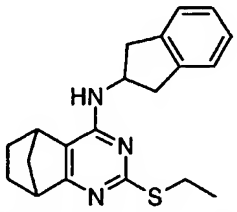


2,6-Dichloro-4-(bicyclo[2.2.1]hept-2-ylamino)quinazoline (0.72 g, 2.3 mmol) and potassium-*tert*-butoxide (280 mg, 2.5 mmol) were dissolved in N-methylpyrrolidinone (5 mL) and stirred at ambient temperature under nitrogen. Methyl mercaptoacetate (0.29 g, 2.7 mmol) was added and the mixture was heated at 85°C for 18 hours. The organic phase was washed with 1M NaOH, dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:5) to give a yellow oil (280 mg). This material was dissolved in methanol/water (9:1)(10 mL), sodium carbonate

(80 mg) was added and the mixture was stirred at room temperature for 18 hours. The mixture poured into 0.1M sodium dihydrogen phosphate and extracted into ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure to give the title compound as a white solid, melting point 155-157°C.

Example 150

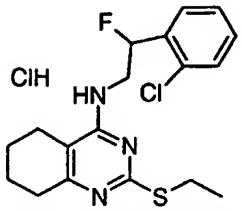
Preparation of N-(2,3-dihydro-1H-inden-2-yl)-4-(ethylthio)-3,5-diazotricyclo[6.2.1.$0^{2,7}$]undeca-2,4,6-trien-6-amine.



S-Ethylisothiouronium bromide (3.7g, 20 mmol) and sodium carbonate (4.3 g, 40.5 mmol) was dissolved in water (70 mL) and stirred at room temperature. Methyl 3-oxobicyclo[2.2.1]heptane-2-carboxylate (3 g, 17.85 mmol) was added and the reaction mixture was stirred for 2 days at room temperature. The precipitate was collected by filtration and dried under high vacuum. A portion of this material was dissolved in chloroform(5 mL), phosphorus oxychloride (6 mL) was added and the reaction mixture was heated to reflux under nitrogen overnight. The reaction mixture was concentrated under reduced pressure, taken up in chloroform and washed with saturated aqueous solution of sodium hydrogen carbonate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure to a dark oil.

Example 151

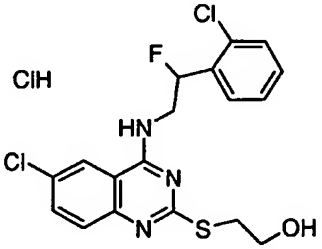
Preparation of N-(2-(2-chlorophenyl)-2-fluoroethyl)-2-(ethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.



2-(2-chlorophenyl)-2-fluoroethylamine (165 mg, 0.95 mmol) (prepared from 2-(2-chlorophenylaziridine)) and 4-chloro-5,6,7,8-tetrahydro-2-ethylthioquinazoline(225 mg, 0.98 mmol) were dissolved in dimethylformamide (10 mL). Diisopropyl ethylamine (300 mg, 2.3 mmol) was added, the mixture was stirred under N_2 and heated at 75°C for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting yellow oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:6) to give a clear oil. This was taken up in ethanol (5 mL), 0.5M ethanolic HCl (2 mL) was then added followed by diethyl ether (30 mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 185-187°C.

Example 152

Preparation of 2-[(6-Chloro-4-{[2-(2-chlorophenyl)-2-fluoroethyl]amino}-2-quinazolinyl)thio]ethanol hydrochloride.

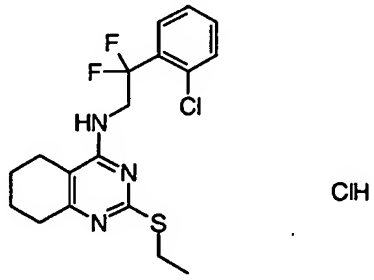


2,4,6-Trichloroquinazoline (300 mg, 1.3 mmol), 2-(2-chlorophenyl)-2-fluoroethylamine (200 mg, 1.1 mmol) and diisopropylethylamine (0.25 g) were dissolved in dimethylformamide (8 mL) and stirred under nitrogen at 75°C for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried

(magnesium sulfate), filtered and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluent ethyl acetate /hexane, 1:4) to give 375 mg of a yellow solid. 240 mg of this material was dissolved in N-methylpyrrolidinone (10 mL) and stirred at ambient temperature under nitrogen. Potassium-*tert*-butoxide (125 mg, 1.1 mmol) was added followed by mercaptoethanol (0.4 mL). The mixture was stirred and heated under nitrogen at 85°C for 18 hours. The reaction mixture was poured into aqueous ammonium chloride solution (70 mL) and extracted into ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:1) to give yellow oil. This was taken up in ethanol (5 mL), 0.5M ethanolic HCl (3 mL) was then added followed by diethyl ether (50 mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 133.5-134.5°C.

Example 153

Preparation of N-(2-(2-chlorophenyl)-2,2-difluoroethyl)-2-(ethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.

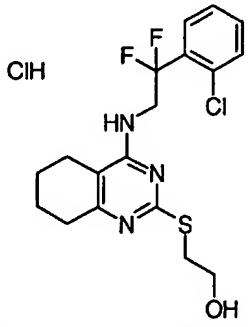


2-(2-chlorophenyl)-2,2-difluoroethylamine (1.6g, 10 mmol)(prepared from 1-(2-chlorophenyl)vinylazide) and 4-chloro-5,6,7,8-tetrahydro-2-ethylthioquinazoline(1.93 g, 8.44 mmol) were dissolved in dimethylformamide (20 mL). Diisopropylethylamine (1.3g, 10 mmol) was added, the mixture was stirred under N_2 and heated at 75°C for 3 days. The mixture was poured into water and extracted with ethyl

acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting yellow oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:6) to give a red oil which was taken up in ethanol (5 mL). 0.5M ethanolic HCl (2 mL) was then added followed by diethyl ether (30 mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 138-140°C.

Example 154

Preparation of N-(2-(2-chlorophenyl)-2,2-difluoroethyl)-2-(2-hydroxyethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.

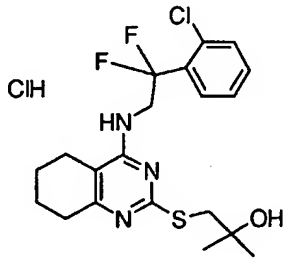


N-(2-(2-chlorophenyl)-2,2-difluoroethyl)-2-(ethylthio)-5,6,7,8-tetrahydroquinazolin-4-amine (0.2 g, 0.52 mmol) was dissolved in acetone/water (19:1)(40 mL) and stirred at ambient temperature. Oxone® (740 mg, 1.2 mmol) dissolved in water (10 mL) was added portionwise to the stirred reaction mixture. When addition was complete the mixture was left to stir at ambient temperature for 18 hours. The mixture was concentrated under reduced pressure and partitioned between ethyl acetate and water. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was dissolved in dimethylformamide (10 mL) and stirred at ambient temperature under nitrogen. Potassium-*tert*-butoxide (100 mg, 0.9 mmol) was added followed by mercaptoethanol (1 mL). The mixture was stirred and heated under nitrogen at 75°C for 18 hours. The reaction mixture was poured into aqueous ammonium

chloride solution (50 mL) and extracted into ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane 4:1) to give a clear oil which was taken up in ethanol (5 mL), 0.5M ethanolic HCl (1 mL) was added followed by diethyl ether (70 mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 133-135°C.

Example 155

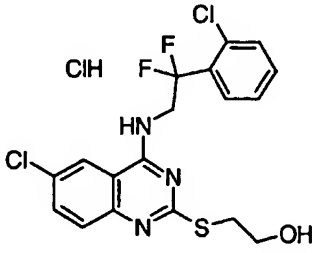
Preparation of N-(2-(2-chlorophenyl)-2,2-difluoroethyl)-2-(2-methyl-2-hydroxypropylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.



Prepared in a similar manner to the above example 154 using 2-hydroxy-2-methylpropanethiol in the second part. Melting point 94-95°C.

Example 156

Preparation of 2-[(6-Chloro-4-{[2-(2-chlorophenyl)-2,2-difluoroethyl]amino}-2-quinazolinyl)thio]ethanol hydrochloride.

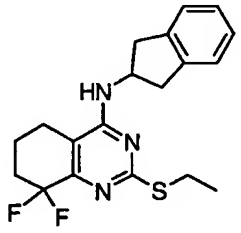


2,4,6-Trichloroquinazoline (300 mg, 1.3 mmol), 2-(2-chlorophenyl)-2-fluoroethylamine (210 mg, 1.1 mmol) and diisopropylethylamine (0.25 g) were dissolved in dimethylformamide (10 mL) and stirred under nitrogen at 75°C

for 18 hours. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluent ethyl acetate /hexane, 1:4) to give 180 mg of a yellow solid. This material was dissolved in dimethylformamide (10 mL) and stirred at ambient temperature under nitrogen. Potassium-*tert*-butoxide (125 mg, 1.1 mmol) was added followed by mercaptoethanol (0.5 mL). The mixture was stirred and heated under nitrogen at 85°C for 18 hours. The reaction mixture was poured into aqueous ammonium chloride solution (70 mL) and extracted into ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:1) to give yellow oil. This was taken up in ethanol (5 mL), 0.5M ethanolic HCl (3 mL) was then added followed by diethyl ether (50 mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 202-203°C.

Example 157

Preparation of N-(2,3-dihydro-1H-inden-2-yl)-2-(ethylthio)-8,8-difluoro-5,6,7,8-tetrahydro-4-quinazolinamine.



(i) Added sodium metal (2.07 g) into ethanol (32 mL) under nitrogen. The mixture was stirred under reflux until all the sodium had dissolved. This mixture was evaporated under vacuum. The pasty mass of sodium ethoxide was cooled and suspended in dry ether (60 mL). Diethyl oxalate (13.15 g, 8.9 mmol) was then added slowly, the orange precipitate

went clear then again to orange, this was followed by the addition of dimethyl adipate (15.7 g, 9.0 mmol). The mixture was stirred for 2 minutes until all the sodium ethoxide had dissolved. The mixture was then allowed to stand for 14 hours. This mixture was then extracted with water (80 mL), and the organic phase was washed with water (40 mL x 2). The combined aqueous phases were acidified to pH 1 with concentrated hydrochloride acid (10 mL) whereupon the product oiled out of solution. The oil was extracted out with diethyl ether. Dried with magnesium sulfate, filtered through a Celite® pad and evaporated under vacuum to produce a yellow oil. This crude product was purified by flash chromatography on silica (eluent: 60% hexane, 40% ethyl acetate) to give trialkyl 2-oxayl adipate as a clear oil.

(ii) Trialkyl 2-oxayl adipate (13.88 g, 5.4 mmol), and 4N hydrochloric acid (65 mL) were heated to 65°C for 10 hours. The mixture was evaporated under vacuum to give a yellow oil. The oil was taken up in a minimum of acetone and diluted with chloroform (200 mL). The solution was diluted with hexane resulting in the precipitation of 2-oxo-heptanedicarboxylic acid as a pale yellow solid which was filtered.

(iii) 2-oxo-heptanedicarboxylic acid (500 mg, 2.87 mmol) was added to a solution of 1,5-diazabicyclo[4.3.0] non-5-ene (392 mg, 3.15 mmol, 1.1eq) in acetone (5 mL). The solution was stirred at 0 °C and dimethyl sulfate (442 mg, 2.87 mmol,) was added dropwise over 5 minutes. The solution was stirred for 3 hours, during which time the solution was allowed to warm to room temperature. The solution was evaporated and washed with 2M hydrochloric acid (10 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic extracts were washed with water (40 mL) and

dried over anhydrous magnesium sulfate, filtered through a Celite® pad and the filtrate was evaporated in 'vacuo' to give 2-oxo-heptanedicarboxylic acid mono methyl ester as a pale yellow oil.

(iv) Added oxalyl chloride (0.371 mL, 0.742 mmol, 1.5 eq) to a stirred solution of 2-oxo-heptanedicarboxylic acid mono methyl ester (100 mg, 0.495 mmol) in chloroform (2 mL) at room temperature for 48 hours. The reaction mixture was evaporated under vacuum. Added methanol (2 mL) with one drop of dimethylformamide and left to stir at room temperature for 5 minutes before the solution was evaporated under vacuum. A yellow oil was obtained of dimethyl 2-oxo-heptanedioate.

(v) To a stirred solution of diethylamino sulfur trifluoride (223 mg, 13.89 mmol, 3eq) in chloroform (3 mL), dimethyl 2-oxo-heptanedioate (100 mg, 4.63 mmol) in chloroform (3 mL) was added dropwise and stirred for 48 hours at room temperature. Water was added (10 mL) and extracted with ethyl acetate (20 mL x 2). The organic layers were combined and dried with anhydrous magnesium sulfate, filtered via a Celite® pad and the filtrate was evaporated under vacuum to produce a yellow oil of dimethyl 2,2-difluoro-heptanedioate.

(vi) To a heated mixture of potassium t-butoxide (23 mg, 0.21 mmol) in toluene (3 mL), dimethyl 2,2-difluoro-heptanedioate (50 mg, 0.21 mmol) in toluene (9 mL) was added dropwise, refluxed overnight, then at room temperature for 48 hours. The reaction mixture was quenched with 2M hydrochloric acid (4 mL) and extracted with diethyl ether (10 mL x 2). The combined organic phases were dried with anhydrous magnesium sulfate and filtered via a Celite® pad. The filtrate was evaporated under vacuum, to obtain a brown oil of methyl 3,3-difluoro-2-oxocyclohexanecarboxylate.

(vii) Methyl 3,3-difluoro-2-oxocyclohexanecarboxylate (99 mg, 5.16 mmol) was added dropwise at room temperature to a stirred solution of aqueous sodium carbonate (1.09 g, 10.3 mmol, 2 eq) in water (35 mL) and S-ethylisothiouronium bromide (1.43 g, 7.73 mmol, 1.5 eq). The mixture was stirred for 24 hours. Acidified with 2N hydrochloric acid from pH 8 to pH 2. Saturated with sodium chloride and extracted with diethyl ether (20 mL x 2). The organic layer was washed with water (30 mL) and the organic layer was dried with anhydrous magnesium sulfate, filtered via a Celite® pad and evaporated under vacuum to obtain a yellow solid. The crude was purified by flash chromatography on silica (eluent, 80% ethyl acetate, 20% hexane) to give 2-(ethylthio)-8,8-difluoro-5,6,7,8-tetrahydro-4-(3H)-quinazolinone.

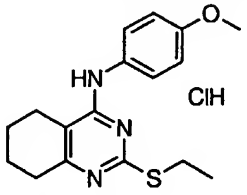
(viii) 2-(ethylthio)-8,8-difluoro-5,6,7,8-tetrahydro-4-(3H)-quinazolinone (210 mg, 0.853 mmol), phosphorus oxychloride (20 mL) and 1,2-dichloroethane (10 mL) were heated to reflux under nitrogen overnight. The reaction mixture was cooled to room temperature, diluted with aqueous sodium hydrogen carbonate (10 mL) and extracted with ethyl acetate (20 mL x 2). Washed the combined organic layers with brine (20 mL), dried the organic phase with anhydrous magnesium sulfate, filtered, via a Celite® pad and evaporated under vacuum to obtain an oil of 4-chloro-2-(ethylthio)-8,8-difluoro-5,6,7,8-tetrahydroquinazoline.

(ix) A mixture of 4-chloro-2-(ethylthio)-8,8-difluoro-5,6,7,8-tetrahydroquinazoline (107 mg, 0.405 mmol), potassium carbonate (111 mg, 0.81 mmol,), 2-aminoindane (60 mg, 0.44 mmol,) and 1-methyl-2-pyrrolindone (10 mL) were heated to 90°C under nitrogen for 24 hours. The reaction mixture was allowed to cool to room temperature. The reaction mixture was poured into water and extracted with

ethyl acetate (20 mL x 2). The organic phase was washed with water, then brine (20 mL x 2). The organic phase dried with magnesium sulfate, filtered and evaporated under vacuum to give the crude product. The crude product was purified by flash chromatography on silica (eluent: 10% hexane, 90% ethyl acetate. Then the product was further purified by prep HPLC using KR100-5C18 column, (80% Acetonitrile/ 20% Water/0.2NH3). A white solid was obtained of the title product (m.p.198-200°C).

Example 158

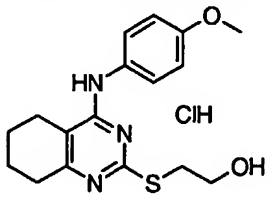
Preparation of 2-(ethylthio)-N-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4-quinazolinamine hydrochloride.



4-chloro-2-(ethylthio)-3,4,5,6,7,8-hexahydroquinazoline (400 mg, 1.75 mmol) as prepared in example 66 (ii) and p-anisidine (237 mg, 1.93 mmol, 1.1 eq), potassium carbonate (241 mg, 1.75 mmol) and 1-methyl-2-pyrrolindone (20 mL) were reacted as in example 66(iii). To give the crude compound. This was purified by flash chromatography on silica (eluent: 40% hexane, 60% ethyl acetate), a brown oil was obtained. The free base was dissolved in ethanol and added dropwise 0.5M ethanolic hydrogen chloride and evaporated under vacuum to give the title compound as a cream solid (m.p.212-213 °C)

Example 159

Preparation of 2-{[4-(4-methoxyanilino)-5,6,7,8-tetrahydro-2-quinazolinyl]thio}ethanol hydrochloride.

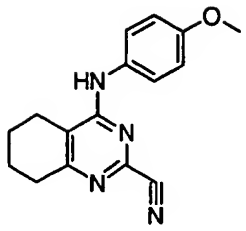


(i) A mixture of 2-(ethylthio)-N-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4-quinazolinamine free base as prepared above (600 mg, 1.9 mmol) and Oxone® (2.92g, 4.75 mmol) in a mixture of acetone: water (19:1) was stirred with a magnetic stirrer for 24 hours at room temperature under nitrogen. The reaction mixture was evaporated under vacuum to the water residue. This residue was then extracted from ethyl acetate (20 mL x 2). The combined organic phases were dried with anhydrous magnesium sulfate, filtered through a Celite® pad and the filtrate evaporated under vacuum to obtain a pale orange solid of 2-(ethylsulfonyl)-N-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4-quinazolinamine.

(ii) A mixture of 2-(ethylsulfonyl)-N-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4-quinazolinamine (380 mg, 1.09 mmol) in 1-methyl-2-pyrrolindone (20 mL) were added to a mixture of potassium butoxide (380 mg) in 1-methyl-2-pyrrolindone (20 mL) and 2-mercaptoethanol (760 mg,) and heated with stirring under nitrogen at 85°C for 5 hours. The reaction mixture was cooled down to room temperature and diluted with aqueous ammonium chloride (20 mL), and extracted with ethyl acetate (20 mL x 2). The combined organic phases were dried with anhydrous magnesium chloride, filtered through a Celite® pad and the filtrate evaporated under vacuum. The crude material was purified with flash chromatography on silica (eluent 10% hexane, 90% ethyl acetate). The hydrochloride salt was formed with 0.5 M ethanolic hydrogen chloride to give the title compound as a white solid (m.p.211-213 °C).

Example 160

Preparation of 4-(4-methoxyanilino)-5,6,7,8-tetrahydro-2-quinazolinecarbonitrile.

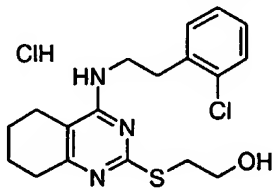


(i) This compound was prepared similarly to 158, but using 2-(methylthio)-N-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4-quinazolinamine; the sulfonyl derivative was prepared as in example 159(i), to obtain N-(4-methoxyphenyl)-2-(methylsulfonyl)-5,6,7,8-tetrahydro-4-quinazolinamine.

(ii) N-(4-methoxyphenyl)-2-(methylsulfonyl)-5,6,7,8-tetrahydro-4-quinazolinamine (600 mg, 1.8 mmol), potassium cyanide (600 mg) in dry dimethylformamide (9 mL) were prepared as in example 70, a cream solid was obtained as the title compound as a free base (m.p.178-180 °C).

Example 161

Preparation of 2-[(4-{[2-chlorophenyl) ethyl]amino}-5,6,7,8-tetrahydro-2-quinazolinyl)thio]ethanol hydrochloride.



(i) N-[2-(2-chlorophenyl)ethyl]-2-(ethylthio)-5,6,7,8-tetrahydro-4-quinazolinamine was prepared as in example 68(i)

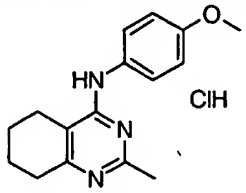
(ii) (N-[2-(2-chlorophenyl)ethyl]-2-(ethylsulfonyl)-5,6,7,8-tetrahydro-4-quinazolinamine was prepared as in example 159(i).

(iii) (N-[2-(2-chlorophenyl)ethyl]-2-(ethylsulfonyl)-5,6,7,8-tetrahydro-4-quinazolinamine, (310 mg, 0.89 mmol), potassium butoxide, 2-mercaptoethanol (0.62 mL) in 1-methyl-2-pyrrolidone (20 mL) was reacted as in example 159(ii), the

hydrochloric salt was made to produce the title compound as a white solid (m.p.198-200°C)

Example 162

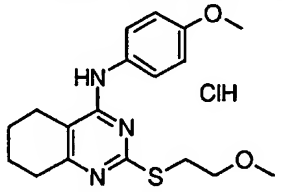
Preparation of N-(4-methoxyphenyl)-2-methyl-5,6,7,8-tetrahydro-4-quinazolinamine hydrochloride.



4-chloro-2-methyl-5,6,7,8-tetrahydroquinazoline (300 mg, 1.64 mmol) as prepared in example 67(ii) was added to p-anisidine(223 mg, 1.81 mmol),potassium carbonate (226 mg,1.64 mmol) in 1-methyl-2-pyrrolindone(20 mL) and prepared as in example 158, the hydrochloride salt was made to obtain the title compound as a white solid (m.p.254-255 °C).

Example 163

Preparation of 2-[(2-methoxyethyl)thio]-N-(4-methoxyphenyl)-5,6,7,8-tetrahydro-4-quinazolinamine hydrochloride.



N-(4-methoxyphenyl)-2-(methylsulfonyl)-5,6,7,8-tetrahydro-4-quinazolinamine (500 mg, 1.5 mmol) was added to potassium butoxide (500 mg) in 1-methyl-2-pyrrolindone (20 mL) and 2-methoxyethanethiol (1.07 g, 11.7 mmol). The procedure was following example 159(ii), to give the title compound (m.p.172-174°C).

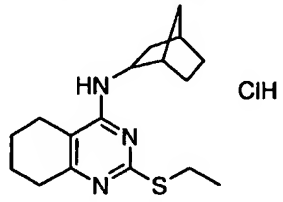
Example 164

Preparation of 4-(2,3-dihydro-1H-inden-2-ylamino)-5,6,7,8-tetrahydro-2-quinazolinecarboxylic acid.

4-(2,3-dihydro-1H-inden-2-ylmethyl)-5,6,7,8-tetrahydroquinazoline-2-carbonitrile (160 mg, 0.55 mmol) as prepared in example 70 as the free base was heated with 2M sodium hydroxide (14 mL) and ethanol (1 mL) at 70 °C for 48 hours. The reaction mixture was cooled to 0 °C and concentrated hydrochloric acid (2 mL) was added slowly. A cream precipitate was observed, this filtered and washed with water (10 mL), collected and dried in the vacuum oven at 40 °C for 6 hours. The title compound was obtained as a cream solid (m.p.168-172 °C).

Example 165

Preparation of N-bicyclo[2.2.1.]hept-2-yl]-2-(ethylthio)-5,6,7,8-tetrahydro-4-quinazolinamine hydrochloride.

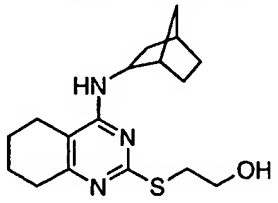


4-chloro-2-(ethylthio)-5,6,7,8-tetrahydroquinzoline (400 mg, 1.75 mmol) as prepared in example 66(ii), 2-aminonorbornane (284 mg, 1.92 mmol) and potassium carbonate (483 mg, 3.5 mmol) in 1-methyl-2-pyrrolindone were heated to 85 °C under nitrogen for 48hours. The reaction mixture was cooled to room temperature. Diluted with ethyl acetate and washed with water (20 mL x 4). The organic phase was dried with anhydrous magnesium sulphate, filtered through a Celite® pad; the filtrate was evaporated under vacuum. The crude material was purified with flash chromatography on silica gel (eluent: 80%hexane, 20% ethyl acetate), the

hydrochloride salt was formed to obtain the title compound (m.p.119-122°C).

Example 166

Preparation of 2-({4-bicyclo[2.2.1]hept-2-ylamino]-5,6,7,8-tetrahydro-2-quinazolinyl}thio)ethanol.



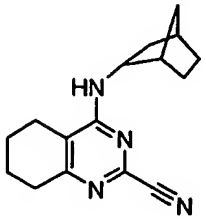
(i) 4-chloro-2-(ethylthio)-5,6,7,8-tetrahydroquinazoline (1.85 g, 8.64 mmol) as prepared in example 66(ii), was reacted with aminonorbornane hydrochloride (1.4 g, 9.5 mmol) and potassium carbonate (2.38g, 17.2 mmol) in 1-methyl-2-pyrrolindinone (100 mL) as in example 9 (i), to obtain N-bicyclo[2.2.1]hept-2-yl-2-(methylthio)-5,6,7,8-tetrahydro-4-quinazolinamine.

(ii) N-bicyclo [2.2.1]hept-2-yl-2-(methylthio)-5,6,7,8-tetrahydro-4-quinazolinamine (1.54 g, 5.3 mmol) was reacted as in example 159(i),to give N-bicyclo[2.2.1]hept-2-yl-2-(methylsulfonyl)-5,6,7,8-tetrahydro-4-quinazolinamine.

(iii) The title compound was prepared as in example 159(ii) with N-bicyclo[2.2.1]hept-2-yl-2- (methylsulfonyl)-5,6,7,8-tetrahydro-4-quinazolinamine (300 mg, 0.93 mmol), potassium butoxide(300 mg), 2-mercaptoethanol (566 mg, 7.2 mmol) in 1-methyl-2-pyrrolindone. A white solid was obtained (m.p.199-200°C).

Example 167

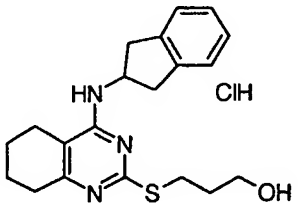
Preparation of 4-bicyclo[2.2.1]hept-2-ylamino]-5,6,7,8-tetrahydro-2-quinazolinecarbonitrile.



N-bicyclo[2.2.1]-hept-2-yl-2-(methylsulfonyl) tetrahydro-4-quinazolineamine was prepared as in example 159(i) and the title compound was prepared as example 70, as a free base, (m.p. 245-246°C)

Example 168

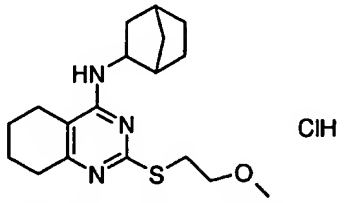
Preparation of 2-{[4-(2,3-dihydro-1H-inden-2-ylamino)-5,6,7,8-tetrahydro-2-quinazolinyl]thio}propanol hydrochloride.



A mixture of N-(2,3-dihydro-1H-inden-2-yl)-2-methylsulfonyl)-5,6,7,8-tetrahydroquinazolin-4-amine (220 mg, 0.641 mmol), and 3-mercapto-1-propanol (460 mg, 0.499 mmol) were treated as in example 159(ii). After purification by flash chromatography on silica, (eluent: 10%hexane, 90% ethyl acetate) the hydrochloride salt was prepared to give the title compound (m.p. 197-199°C).

Example 169

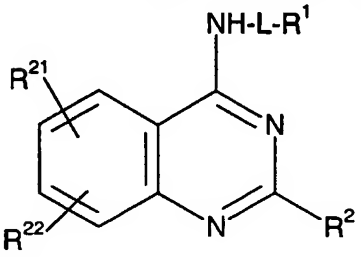
Preparation of N-[(bicyclo[2.2.1]hept-2-yl]-2-[(2-methoxyethyl)thio]-5,6,7,8-tetrahydro-4-quinazolinamine hydrochloride.



N-bicyclo[2,2,1]hept-2-yl-2-(ethylsulfonyl)-tetrahydro-4-quinazolinamine (300 mg, 0.934 mmol) was prepared in the similar manner as 159(i) from the corresponding ethylthio, and then reacted using 2-methoxyethanethiol (670 mg,7.29 mmol), by the method in example 159(ii), the crude compound was purified by prep HPLC (KR100-5C18), (80% Acetonitrile /20% Water/0.2% NH_3), the hydrochloride salt was prepared to obtain the title compound (m.p.133-135 °C).

Examples 170 to 172

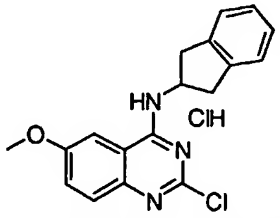
These were prepared by the method described in example 12



$R^{21}R^{22}$	R^2	L-R^1	Ex	m.p. (°C)	Salt form
6-Methoxy	Methyl	2-(2-Chlorophenethyl)	170	232-35	HCl
6-Methoxy	Trifluoro-methyl	2-(2,6-Dichlorophenethyl)	171	180-2	HCl
6-Methoxy	Trifluoro-methyl	2-(2-Chlorophenethyl)	172	174-6	HCl

Example 173

Preparation of 2-Chloro-4-(2,3-dihydro-1H-inden-2-ylamino)-6-methoxyquinazoline hydrochloride.

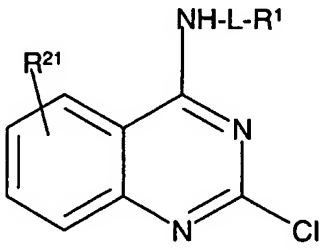


A mixture of 2,4-dichloro-6-methoxyquinazoline (170 mg, 0.8 mmol), 2-aminoindane (107 mg, 0.8 mmol) and diisopropylethylamine (0.695 mL, 4 mmol) in dry dimethylformamide (10 mL) was stirred at ambient temperature for 24 hours. Additional 2-aminoindane (15 mg, 0.11 mmol) was added and stirring continued for 4 hours. The reaction mixture was poured into water and extracted with ethyl acetate (3x). The combined organic extracts were washed sequentially with water and saturated sodium chloride

solution, then dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product as a pink oily solid. The crude product was purified by flash chromatography on silica (eluent diethyl ether) to give the free base of the title compound as a white solid. The free base was dissolved in 0.5 molar ethanolic hydrogen chloride and evaporated *in vacuo* to give the title compound as a white solid (m.p. 240-2°C).

Examples 174 to 177

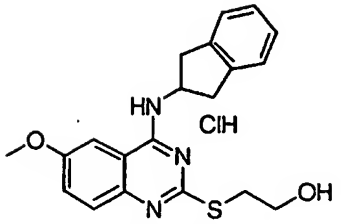
The compounds of examples 174 to 177 were prepared following the method of example 173.



R^{21}	$L-R^1$		m.p. (°C)	Salt form
6-Methoxy	4-Methoxyphenyl	174	230-2	HCl
6-Methoxy	Bicyclo[2.2.1]hept-2-yl	175	203-5	HCl
6-Methoxy	2-(2-Chlorophenyl)	176	187-8	HCl
6-Chloro	2-(2-Chlorophenyl)	177	212-14	HCl

Example 178

Preparation of 2-(2-Hydroxyethylthio)-4-(2,3-dihydro-1H-inden-2-ylamino)-6-methoxyquinazoline hydrochloride.



A mixture of 2-mercaptoethanol (0.082 mL, 1.17 mmol) and potassium-tertiary butoxide (131 mg, 1.17 mmol) in dry dimethylformamide (2 mL) was stirred at ambient temperature for 10 minutes, then a solution of 2-chloro-4-(2-indanylamino)-6-methoxyquinazoline (120 mg, 0.39 mmol) in dry dimethylformamide (2 mL) was added. The reaction mixture was stirred, under nitrogen, at 90°, for 2 hours. The reaction mixture was allowed to cool, poured into water (100 mL), and extracted with ethyl acetate (3x). The combined organic extracts were washed sequentially with water and saturated sodium chloride solution, then dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product as a white oil. The crude product was purified by flash chromatography on silica (eluent diethyl ether) to give the free base of the title compound as a white solid. The free base was dissolved in 0.5 molar ethanolic hydrogen chloride and evaporated *in vacuo* to give the title compound as a white solid (m.p. 148°C dec.).

Examples 179 to 188

The compound of examples 179 to 188 were prepared following the method of examples 173 and 178. Thiol side chains used in the preparation of some of the examples were prepared as follows:

2-Methoxyethanethiol

A mixture of 2-chloroethyl methyl ether (50 g, 530 mmol) and thiourea (40.26 g, 530 mmol) in 95% ethanol (250 mL) was heated at reflux under nitrogen for 24 hours. The cooled ethanol solution was evaporated *in vacuo* to low volume at 45°C, the residue dissolved in a solution of

sodium hydroxide (30.6 g) in water (300 mL) and the solution heated at reflux under nitrogen for 2 hours. The cooled solution was then acidified with dilute sulfuric acid (7 mL of concentrated sulfuric acid in 50 mL of water) and extracted with diethyl ether (2x), under a nitrogen atmosphere. The combined organic extracts were dried over magnesium sulfate, filtered and evaporated *in vacuo* at 35°C, to give the product as a yellow oil. (Stored under a nitrogen atmosphere).

The amine starting material used in the preparation of the compound of example 185 was prepared as follows:

(i) 2-(2-Chlorophenyl)-2-methylpropanenitrile

To a stirred suspension of 60% sodium hydride (pre-washed with petroleum spirit b.p.40-60°C) (6.1 g, 198 mmol) in dry dimethylformamide (100 mL) under nitrogen and cooled to 5°C was added, dropwise, a solution of (2-chlorophenyl) acetonitrile (10 g, 66 mmol) in dry dimethylformamide (20 mL). The reaction mixture allowed to warm to ambient temperature and stirred for 45 minutes. The reaction mixture was then re-cooled to 5°C and a solution of iodomethane (12.3 mL, 198 mmol) in dry dimethylformamide (20 mL) was added dropwise. The reaction mixture was allowed to warm to ambient temperature and stirred for a further 2 hours. The reaction mixture was quenched with water and extracted with ethyl acetate (3x). The combined organic extracts were washed sequentially with water (2x) and saturated sodium chloride solution, then dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the product as a yellow oil.

(ii) 2-(2-chlorophenyl)-2-methylpropylamine

To zirconium tetrachloride (18.82 g, 80.7 mmol) in a flame-dried flask was cautiously added dry tetrahydrofuran (100 mL). To the pink suspension was added, portionwise, sodium borohydride (3.07 g, 80.7 mmol), followed by dropwise addition of a solution of 2-(2-chlorophenyl)-2-

methylpropanenitrile (11.6 g, 64.6 mmol) in dry tetrahydrofuran (20 mL). The reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was cooled to 5°C, cautiously quenched with water (250 mL), basified with 2 molar sodium hydroxide and extracted with diethyl ether (3x). The combined organic extracts were washed sequentially with water and saturated sodium chloride solution, then dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product as a yellow oil. The crude product was purified by fractional distillation to give the product as a clear oil (b.p. 240°C /2.8mbar).

The amine starting material used in the preparation of the compound of example 186 was prepared as follows:

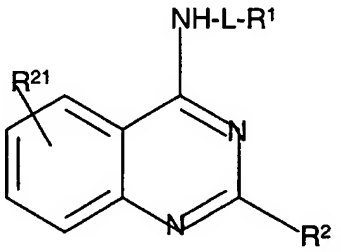
(i) 2-(2-chlorophenyl)propanenitrile

A mixture of (2-chlorophenyl) acetonitrile (5.0 g, 33 mmol), potassium carbonate (5.0 g, 36.2 mmol) and dimethyl carbonate (53.43 g, 594 mmol) was stirred in a sealed vessel at 180°C for 72 hours. The reaction mixture was allowed to cool, filtered, the filter cake washed with methanol and the combined filtrates and washings evaporated *in vacuo* to give an oil. The oil was partially dissolved in dichloromethane, the insoluble portion filtered and the filtrates evaporated *in vacuo* to give the crude product as an amber oil. The crude product was purified by fractional distillation to give the product as a clear oil.

(ii) 2-(2-Chlorophenyl)-1-propanamine

To zirconium tetrachloride (5.28 g, 22.6 mmol) in a flame-dried flask was cautiously added dry tetrahydrofuran (40 mL). To the pink suspension was added, portion wise, sodium borohydride (0.86 g, 22.6 mmol), followed by dropwise addition of a solution of 2-(2-chlorophenyl)propanenitrile (3.0 g, 18.12 mmol) in dry tetrahydrofuran (20 mL).

The reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was cooled to 5°C, cautiously quenched with water (250 mL), basified with 2 molar sodium hydroxide and extracted with diethyl ether (3x). The combined organic extracts were washed sequentially with water and saturated sodium chloride solution, then dried over magnesium sulfate, filtered and evaporated *in vacuo* to give the crude product as a yellow oil. The crude product was purified by distillation in a bulb to bulb apparatus to give the product as a clear oil (b.p. 110°C / 2.0mbar).

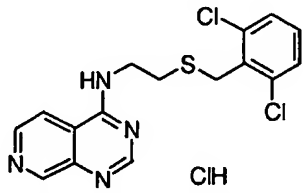


R^{21}	R^2	L-R^1	Ex	m.p. (°C)	Salt form
6-Methoxy	2-Hydroxy-ethylthio	4-Methoxyphenyl	179	260 (dec.)	HCl
6-Methoxy	2-Hydroxy-ethylthio	Bicyclo[2.2.1]hept-2-yl	180	204-8	HCl
6-Methoxy	2-Hydroxy-ethylthio	2-(2-chlorophenyl)	181	129-131	HCl
6-Methoxy	2-methoxy-ethylthio	4-Methoxyphenyl	182	250 (dec.)	HCl
6-Chloro	2-Hydroxy-ethylthio	2-(2-Chlorophenyl)	183	216-18	HCl

6-Chloro	2-methoxy-ethylthio	2-(2-Chlorophenyl)	184	195-7	HCl
6-Chloro	2-Hydroxy-ethylthio	2,2-Dimethyl-2-(2-chlorophenyl)	185	208-10	HCl
6-Chloro	2-Hydroxy-ethylthio	2-Methyl-2-(2-chlorophenyl)	186	120 (dec.)	HCl
6-Chloro	2-Hydroxy-ethylthio	Bicyclo[2.2.1]hept-2-yl	187	156-60	HCl
6-Chloro	2-methoxy-ethylthio	Bicyclo[2.2.1]hept-2-yl	188	250 (dec.)	HCl

Example 189

Preparation of 4-{2-[(2,6-Dichlorobenzyl)thio]ethylamino}pyrido[3,4-d]pyrimidine hydrochloride.



(i) A mixture of 3-aminopyridine-4-carboxylic acid (4.03 g, 29.2 mmol) and formamide (50 mL) was stirred at 140°C for 2 hours, and then at 150°C for 16 hours. The reaction mixture was allowed to cool and the resultant precipitate collected by filtration, washed with water on the sinter and dried *in vacuo* to give pyrido[3,4-d]pyrimidin-4(3H)-one as a brown crystalline solid.

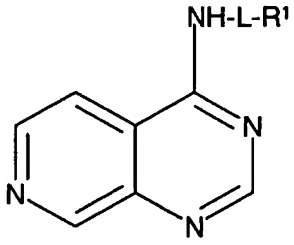
(ii) A mixture of pyrido[3,4-d]pyrimidin-4(3H)-one (1.49 g, 10.1 mmol) and phosphorus oxychloride (40 mL) was stirred at reflux for 16 hours. The reaction mixture was allowed to cool, evaporated *in vacuo* and dissolved in ethyl acetate. The ethyl acetate was evaporated *in vacuo* and the residue suspended in ethyl acetate. The suspension was

filtered, the filtrate dried over magnesium sulfate, filtered and evaporated *in vacuo* to give 4-chloro-pyrido[3,4-d]pyrimidine as a yellow solid.

(iii) A solution of 4-chloro-pyrido[3,4-d]pyrimidine (340 mg, 1.7 mmol), 2-(2,6-dichlorobenzylthio)ethylamine (477 mg, 2.02 mmol) and diisopropylethylamine (2.17 g, 17 mmol) in ethanol (20 mL) was stirred at ambient temperature for 16 hours. The reaction mixture was evaporated *in vacuo* to give the crude product as a yellow oil. The crude product was purified by flash chromatography on silica (eluent diethyl ether then diethyl ether 50% ethyl acetate 50%) to give the free base of the title compound as a yellow gum. The free base was dissolved in 0.5M ethanolic hydrogen chloride and evaporated *in vacuo* to give the title compound as a white solid. (m.p. 145-150°C).

Example 190

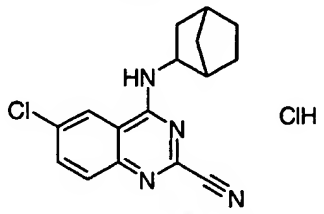
The compound of example 190 was prepared by the method of example 189.



L-R¹		m.p. (°C)	
2-(2,6-Dichlorophenyl)	190	208-10	HCl

Example 191

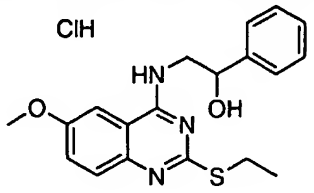
Preparation of 4-(Bicyclo[2.2.1]hept-2-ylamino)-6-chloro-2-cyanoquinazoline hydrochloride.



(i) A stirred mixture of 4-(bicyclo[2.2.1]hept-2-ylamino)-6-chloro-2-ethylthioquinazoline hydrochloride salt (0.20g, 0.53 mmol) and Oxone® (1.6 g, 2.60 mmol) in acetone (27 mL) and water (3 mL) at room temperature for 3 days. The acetone was removed in vacuo and the concentrate diluted with water and made basic with 2M aqueous sodium hydroxide. Extracted with dichloromethane, dried extract over magnesium sulfate, filtered and evaporated to give 4-(bicyclo[2.2.1]hept-2-ylamino)-6-chloro-2-ethylsulphonylquinazoline contaminated with the 2-hydroxy derivative as a colorless solid.

(ii) A suspension of 4-(bicyclo[2.2.1]hept-2-ylamino)-6-chloro-2-ethylsulphonylquinazoline and its contaminant (0.10 g, 0.27 mmol) and potassium cyanide (0.10g, 1.53 mmol) in dried dimethylformamide (1.5 mL) was heated with stirring under an atmosphere of nitrogen at 100°C for 17h. The resulting red solution was cooled, diluted with water and extracted twice with ethyl acetate. The extracts were washed with water (5X) and brine, dried over magnesium sulfate, filtered and evaporated to a solid. Purified solid on flash silica eluting with hexane-ethyl acetate (7:1) to give 4-(bicyclo[2.2.1]hept-2-ylamino)-6-chloro-2-cyanoquinazoline as a colorless solid. The solid was dissolved in warm dioxan, treated with hydrogen chloride in dioxan and precipitated by addition of diethyl ether to give the title compound. Mp 229-236°C, m.s. m/e 297/299

Example 192
Preparation of 4-{[2-hydroxy(2-phenyl)ethyl]amino}-6-methoxy-2-(ethylthio)quinazoline hydrochloride.

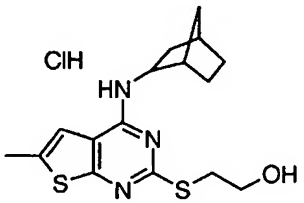


(i) 2-amino-1-phenylethanol (0.73 g, 5.3 mmol) was added to a stirred suspension of 2,4-dichloro-6-methoxy-quinazoline (1.2 g, 5.3 mmol)and diisopropylethylamine (3.4 mL, 20 mmol) in dried dimethylformamide (10 mL) at room temperature under nitrogen. After 1h, iced water (30 mL) was added and extracted with ethyl acetate (30 mL). The extract were washed with water (30 mL), brine (2 x 30 mL), dried, filtered and evaporated to a yellow viscous oil (1.90 g). Trituration with diethyl ether (20 mL) gave a pale yellow solid of 2-chloro-4-{[2-hydroxy(2-phenyl)ethyl]amino}-6-methoxy-quinazoline.

(ii) A mixture of 2-chloro-4-{[2-hydroxy(2-phenyl)ethyl]amino}-6-methoxy-quinazoline (0.33g 1 mmol) and sodium ethylthiolate (0.68 g, 8 mmol) in dried dimethylformamide (3 mL) was stirred at room temperature for 48h. After diluting with water (15 mL), the mixture was extracted with ethyl acetate (15 mL). The extracts were washed with water (10 mL), brine (2x 10 mL), dried, filtered and evaporated to a yellow oil. Triturated with diethyl ether (5 mL) gave a yellow solid (0.29 g). Converted to the hydrochloride salt by dissolving in ethanol (4 mL) and adding hydrogen chloride (0.5 M solution in ethanol 1.6 mL) to crystallize the title compound as a pale yellow solid mp 212-213°C.

Example 193

Preparation of 4-(Bicyclo[2.2.1]hept-2-ylamino)-2-(2-hydroxyethylthio)-6-methyl-thieno[2,3-d]pyrimidine hydrochloride.



(i) A stirred suspension of 2,4-hydroxy-6-methyl-thieno[2,3-d]pyrimidine (11.3 g, 62 mmol and phosphorus oxychloride (100 mL) was heated under reflux for 20h. The mixture was evaporated, the black residue suspended in ethyl acetate (300 mL) and washed with 2M aqueous sodium carbonate (2x 300 mL), then brine (300 mL). The ethyl acetate solution was dried, filtered and evaporated to a brown solid of 2,4-dichloro-6-methyl-thieno[2,3-d]pyrimidine.

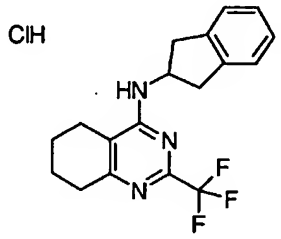
(ii) A mixture of 2,4-dichloro-6-methyl-thieno[2,3-d]pyrimidine (0.47 g, 2.1 mmol), exo-2-aminonorbornane (0.24 g, 2.1 mmol) and ethyl diisopropylethylamine (1.5 mL, 8.4 mmol) in dried dimethylformamide (5 mL) was stirred at room temperature for 24h. The mixture was evaporated to a small volume, diluted with water (30 mL) and extracted with ethyl acetate (30 mL). The extracts were washed with brine (2 x 30 mL), dried, filtered and evaporated to a yellow glass. The crude product was purified by flash chromatography on silica eluting with 2:1 diethyl ether: n-hexane to give a yellow foam of 4-(bicyclo[2.2.1]hept-2-ylamino)-2-chloro-6-methyl-thieno[2,3-d]pyrimidine.

(iii) A solution of 4-(bicyclo[2.2.1]hept-2-ylamino)-2-chloro-6-methyl-thieno[2,3-d]pyrimidine (0.24 g, 0.82 mmol) in dried dimethylformamide (2 mL) was added to a stirred mixture of 2-mercaptoethanol (0.19 g, 2.45 mmol) and potassium t-butoxide (0.27 g, 2.45 mmol) in dried dimethylformamide (3 mL). After heating to 90°C for 3h, the

mixture was cooled, diluted with water (15 mL) and extracted with ethyl acetate (20 mL). The extracts were washed with saturated aqueous sodium bicarbonate (15 mL), brine (15 mL), dried, filtered and evaporated to a white solid (0.27 g). The crude product was purified by flash chromatography on silica eluting with ethyl acetate to give a white solid. This was dissolved in ethanol (2 mL) and acidified with ethanolic hydrogen chloride (0.5 M, 2 mL) to crystallize the title product mp 235-237°C.

Example 194

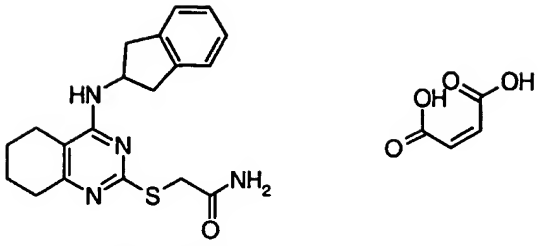
Preparation of N-(2,3-dihydro-1H-inden-2-yl)-2-trifluoromethyl-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.



4-Chloro-5,6,7,8-tetrahydro-2-trifluoromethylquinazoline (400 mg, 1.7 mmol) and 2-aminoindane (250 mg, 1.8 mmol) were dissolved in dimethylformamide (10 mL). Diisopropylethylamine (300 mg, 2.3 mmol) was added, the mixture was stirred under N_2 and heated at 80°C for 1 hour. The mixture was poured into water and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting dark oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:3) to give a dark oil which was taken up in ethanol (5 mL). 0.5M ethanolic HCl (4 mL) was then added followed by diethyl ether (30 mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 137-138 °C.

Example 195

Preparation of N-(2-((4-(2,3-dihydro-1H-inden-2-ylamino)-5,6,7,8-tetrahydroquinazolin-2-yl)thio)acetamide maleate.

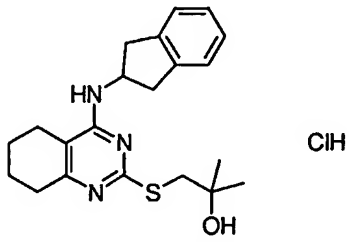


N-(2,3-dihydro-*1H*-inden-2-yl)-2-(methylsulfonyl)-5,6,7,8-tetrahydroquinazolin-4-amine (660 mg, 1.85 mmol) was dissolved in N-methylpyrrolidinone (15 mL) and stirred at ambient temperature under nitrogen. Potassium-*tert*-butoxide (265 mg, 2.36 mmol) was added followed by methylthioglycolate (200 mg, 1.88 mmol). The mixture was stirred and heated under nitrogen at 90°C for 18 hours. The reaction mixture was poured into aqueous ammonium chloride solution (150 mL) and extracted into ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was taken up in methanol/water (9:1)(20 mL), sodium hydrogen carbonate (400 mg) was added and the mixture was stirred for four days at ambient temperature. The reaction mixture was concentrated under reduced pressure and partitioned between water and ethyl acetate. The aqueous phase was acidified to pH4 and extracted with ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure to give 530 mg of dark oil. The resulting oil was taken up in THF and stirred at ambient temperature under nitrogen. Carbonyl diimidazole (250 mg, 1.5 mmol) was added and the reaction mixture was stirred for three hours then ammonia (0.5M in dioxan)(10 mL) was added. Stirring was continued overnight then the reaction mixture was concentrated under reduced pressure and partitioned between water and ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure then purified by column chromatography on silica gel (eluent ethyl acetate) to give N-(2-((4-(2,3-dihydro-1*H*-inden-2-ylamino)-5,6,7,8-tetrahydro quinazolin-2-

yl)thio)acetamide as a yellow oil (60 mg). This was taken up in ethyl acetate, maleic acid (20 mg) was added, the mixture was heated briefly and then allowed to cool. A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 152.5-153.5°C.

Example 196

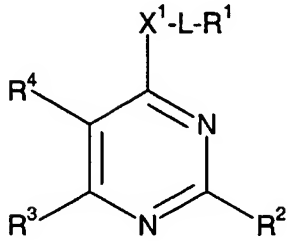
Preparation of N-(2,3-dihydro-1H-inden-2-yl)-2-(2-methyl-2-hydroxypropylthio)-5,6,7,8-tetrahydroquinazolin-4-amine hydrochloride.



N-(2,3-dihydro-*1H*-inden-2-yl)-2-(methylsulfonyl)-5,6,7,8-tetrahydroquinazolin-4-amine (575 mg, 1.67 mmol) was dissolved in N-methylpyrrolidinone (15 mL) and stirred at ambient temperature under nitrogen. Potassium-*tert*-butoxide (500 mg, 4.4 mmol) was added followed by 2-methyl-2-hydroxypropanethiol (500 mg, 4.7 mmol). The mixture was stirred and heated under nitrogen at 90°C for 18 hours. The reaction mixture was poured into aqueous ammonium chloride solution (150 mL) and extracted into ethyl acetate. The organic phase was dried (magnesium sulfate), filtered and concentrated under reduced pressure. The resulting oil was purified by column chromatography on silica gel (eluent ethyl acetate/hexane, 1:4) to give a yellow oil which was taken up in ethanol (5 mL), 0.5M ethanolic HCl (4 mL) was added followed by diethyl ether (70 mL). A white solid crystallized on standing and was collected by filtration to give the title compound, melting point 111.5-112.5°C.

WHAT IS CLAIMED IS:

1. The use of a compound of general formula



in which:

X^1 represents O or NH;

L represents a bond or a (1-6C)alkylene chain optionally interrupted by O, S, SO, SO_2 or NH and optionally substituted on an alkylene carbon atom by fluoro, hydroxy, (1-4C)alkoxy or oxo;

R^1 represents an unsubstituted or substituted carbocyclic or heterocyclic group;

R^2 represents a hydrogen atom, a halogen atom, a carboxyl group, a cyano group, a SCH_2CN, or a group of formula X^2-R^5 in which X^2 represents a bond, O, S, SO, SO_2 or NH and R^5 represents (1-8C)alkyl, (3-10C)cycloalkyl, halo(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkanoyl(1-4C)alkyl, (1-4C)alkanoyloxy(1-4C)alkyl, carboxy(1-4C)alkyl, (1-4C)alkylaminocarbonyl(1-4C)alkyl, (1-4C)alkanoylamino, (1-4C)alkanoylamino(1-4C)alkyl, (1-4C)alkanoylamino[(1-4C)alkyl]$_2$, (1-4C)alkylthio(1-4C)alkyl, (1-4C)alkylsulfinyl(1-4C)alkyl, (1-4C)alkylsulfonyl(1-4C)alkyl, (1-4C)alkylsulfonylamino)(1-4C)alkyl, (1-4C)alkylamino-sulfonyl)(1-4C)alkyl, di(1-4C)alkylaminophosphonyl)(1-4C)alkyl, phenyl or phenyl(1-4C)alkyl in which any phenyl group is unsubstituted or substituted by one or two substituents selected

independently from a halogen atom, (1-4C)alkyl and (1-4C)alkoxy; and

R^3 and R^4 each independently represents (1-4C)alkyl or together with the carbon atoms to which they are attached form an unsubstituted or substituted carbocyclic or heterocyclic ring;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for the treatment of a condition indicating administration of an mGluR1 antagonist.

2. Use as claimed in Claim 1, in which X^1 represents NH.

3. Use as claimed in Claim 1 or Claim 2, in which L represents a bond or a group of formula $C_mH_{2m}-(X_3)_q-C_nH_{2n}$ in which X^3 is O, S, SO, SO_2, NH, CHF, CF_2, CHOH, CH(O(1-4C)alkyl) or CO, q is 0 or 1, and each of m and n is 0 or an integer of from 1 to 4, provided that when q is 1 and X^3 is O, S, SO, SO_2 or NH, m is at least 2.

4. Use as claimed in Claim 3, in which L represents a bond, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)CH_2-$, $-(CH_2)_2SCH_2-$, $-(CH_2)_2)SO_2CH_2-$, $-CH(CH_2CH_3)CH_2OCH_2-$, $-CH_2CHF-$, $-CH_2CF_2-$, $-CH_2CH(OH)-$ and $-CH_2CO-$.

5. Use as claimed in any one of Claims 1 to 4, in which R^1 represents an unsubstituted or substituted carbocyclic group in which the carbocyclic group is selected from an aromatic group, a non-aromatic group and a non-aromatic group fused with an aromatic group.

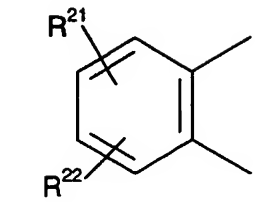
6. Use as claimed in Claim 5, in which the carbocyclic group is selected from phenyl which is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a

(1-4C)alkoxy group; (3-10C)cycloalkyl which is unsubstituted or substituted by from one to three methyl groups; 2,3-dihydro-1H-indenyl; and 1,2,3,4-tetrahydronaphthyl.

7. Use as claimed in Claim 6, in which R^1 represents phenyl, 2-chlorophenyl, 3-bromophenyl, 2,6-dichlorophenyl, 2-methylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 4-phenylphenyl, cyclohexyl, bicyclo[2.2.1]hept-2-yl, (1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-2-yl, adamantyl, 2,3-dihydro-1H-inden-1-yl, 2,3-dihydro-1H-inden-2-yl and 1,2,3,4-tetrahydronaphth-1-yl.

8. Use as claimed in any one of Claims 1 to 7, in which R^2 represents a hydrogen atom, a halogen atom, a carboxy group, a cyano group, or a (1-8C)alkyl, halo(1-6C)alkyl, (1-6C)alkoxy, hydroxy(1-6C)alkoxy, (1-6C)alkylthio, (1-4C)alkylsulfonyl, (1-4C)alkylamino, halo(1-4C)alkylthio, hydroxy(1-4C)alkylthio, dihydroxy(1-4C)alkylthio, (1-4C)alkoxy(1-4C)alkylthio, (1-4C)alkanoyl(1-4C)alkylthio, (1-4C)alkoxycarbonyl(1-4C)alkylthio, carboxy(1-4C)alkylthio, (1-4C)alkylaminocarbonyl(1-4C)alkylthio, (1-4C)alkanoylamino(1-4C)alkylthio, (1-4C)alkylaminosulfonyl)(1-4C)alkylthio, di(1-4C)alkylaminophosphonyl)(1-4C)alkylthio, or phenyl(1-4C)alkylthio in which the phenyl group is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, (1-4C)alkyl and (1-4C)alkoxy.

9. Use as claimed in any one of Claims 1 to 8 in which R^3 and R^4 together with the carbon atoms to which they are attached form a ring of formula:



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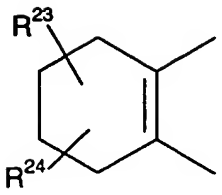

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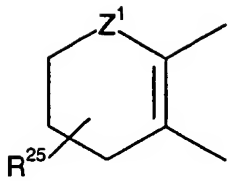

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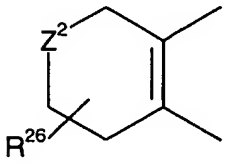

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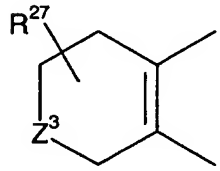

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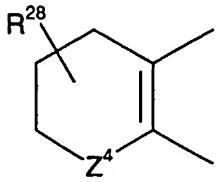

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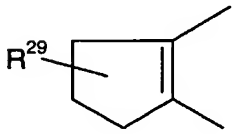

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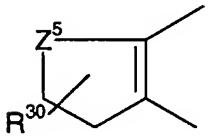

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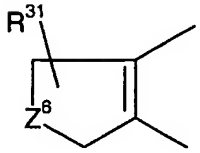

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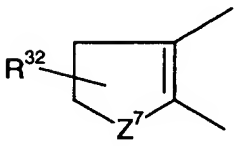

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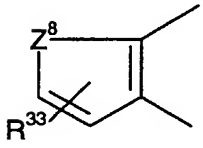

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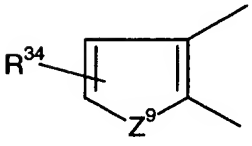

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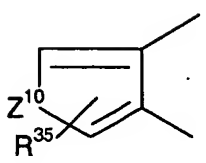

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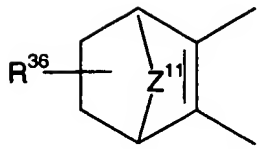

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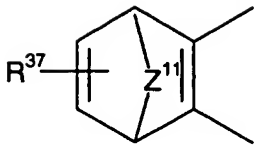

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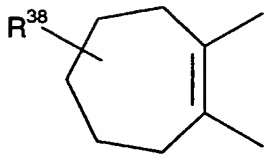


p

in which:

Z^1, Z^2, Z^3, Z^4, Z^5, Z^6, Z^7, Z^8, Z^9 and Z^{10} are each selected independently from O, NR^{41}, S, SO and SO_2;

Z^{11} represents O, S, CH_2 or CH_2CH_2;

R^{21} and R^{22} each independently represents a hydrogen atom, a halogen atom, a nitro group, a cyano group, a (1-4C)alkyl group, a halo(1-4C)alkyl group, or a group of formula $-X^4-R^{51}$ in which X^4 represents O, S, SO, SO_2, NR^{52}, CO, COO, OCO, CONH, NHCO, SO_2NH, or $NHSO_2$ and R^{51} represents a hydrogen atom, a (1-4C)alkyl group, a phenyl group or a phenyl(1-4C)alkyl group in which any phenyl group is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a (1-4C)alkoxy group;

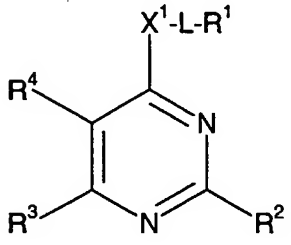
R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{36}, R^{37} and R^{38} each independently represents a hydrogen atom, an oxo group, a halogen atom, a (1-4C)alkyl group, a halo(1-4C)alkyl group, an aryl(1-4C)alkyl group, a (1-4C)alkoxy(1-4C)alkyl group, a (1-4C)alkylthio group, a (1-4C)alkylsulfinyl group, a (1-4C)alkylsulfonyl group or a (1-4C)alkanoyl group;

R^{33}, R^{34} and R^{35} each independently represents a hydrogen atom, a halogen atom, a (1-4C)alkyl group or a (1-4C)alkoxy group;

R^{41} represents a (1-6C)alkyl group or a group of formula Y-R^a in which Y represents CO, COO or CONH and R^a represents (1-4C)alkyl, phenyl(1-4C)alkyl, phenyl(2-4C)alkenyl, (3-10C)cycloalkyl, or, when Y is CO, morpholino; and

R^{52} represents a hydrogen atom, a (1-4C)alkyl group or a phenyl(1-4C)alkyl group.

10. A method of antagonizing the action of glutamate at mGluR1 receptors in a patient requiring such treatment, which comprises administering an effective amount of a compound of general formula



I

in which:

X^1 represents O or NH;

L represents a bond or a (1-6C)alkylene chain optionally interrupted by O, S, SO, SO_2 or NH and optionally substituted on an alkylene carbon atom by fluoro, hydroxy, (1-4C)alkoxy or oxo;

R^1 represents an unsubstituted or substituted carbocyclic or heterocyclic group;

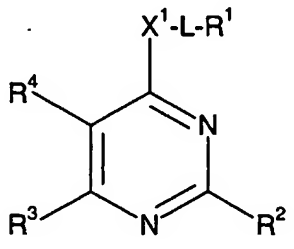
R^2 represents a hydrogen atom, a halogen atom, a carboxyl group, a cyano group or a group of formula X^2-R^5 in which X^2 represents a bond, O, S, SO, SO_2 or NH and R^5 represents (1-8C)alkyl, (3-10C)cycloalkyl, halo(1-6C)alkyl, hydroxy(1-

6C)alkyl, dihydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkanoyl(1-4C)alkyl, (1-4C)alkanoyloxy(1-4C)alkyl, carboxy(1-4C)alkyl, (1-4C)alkylaminocarbonyl(1-4C)alkyl, (1-4C)alkanoylamino(1-4C)alkyl, (1-4C)alkanoylamino[(1-4C)alkyl]$_2$, (1-4C)alkylthio(1-4C)alkyl, (1-4C)alkylsulfinyl(1-4C)alkyl, (1-4C)alkylsulfonyl(1-4C)alkyl, (1-4C)alkylsulfonylamino)(1-4C)alkyl, (1-4C)alkylamino-sulfonyl)(1-4C)alkyl, di(1-4C)alkylaminophosphonyl)(1-4C)alkyl, phenyl or phenyl(1-4C)alkyl in which any phenyl group is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, (1-4C)alkyl and (1-4C)alkoxy; and

R^3 and R^4 each independently represents (1-4C)alkyl or together with the carbon atoms to which they are attached form an unsubstituted or substituted carbocyclic or heterocyclic ring;

or a pharmaceutically acceptable salt thereof.

11. A compound of general formula



I

in which:

X^1 represents O or NH;

L represents a bond or a (1-6C)alkylene chain optionally interrupted by O, S, SO, SO_2 or NH and optionally substituted on an alkylene carbon atom by fluoro, hydroxy, (1-4C)alkoxy or oxo;

R^1 represents an unsubstituted or substituted carbocyclic or heterocyclic group;

R^2 represents a hydrogen atom, a halogen atom, a carboxyl group, a cyano group, a SCH_2CN, or a group of formula X^2-R^5 in which X^2 represents a bond, O, S, SO, SO_2 or NH and R^5 represents (1-8C)alkyl, (3-10C)cycloalkyl, halo(1-6C)alkyl, hydroxy(1-6C)alkyl, dihydroxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, (1-4C)alkanoyl(1-4C)alkyl, (1-4C)alkanoyloxy(1-4C)alkyl, carboxy(1-4C)alkyl, (1-4C)alkylaminocarbonyl(1-4C)alkyl, (1-4C)alkanoylamino, (1-4C)alkanoylamino(1-4C)alkyl, (1-4C)alkanoylamino[(1-4C)alkyl]$_2$, (1-4C)alkylthio(1-4C)alkyl, (1-4C)alkylsulfinyl(1-4C)alkyl, (1-4C)alkylsulfonyl(1-4C)alkyl, (1-4C)alkylsulfonylamino)(1-4C)alkyl, (1-4C)alkylamino-sulfonyl)(1-4C)alkyl, di(1-4C)alkylaminophosphonyl)(1-4C)alkyl, phenyl or phenyl(1-4C)alkyl in which any phenyl group is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, (1-4C)alkyl and (1-4C)alkoxy; and

R^3 and R^4 each independently represents (1-4C)alkyl or together with the carbon atoms to which they are attached form an unsubstituted or substituted carbocyclic or heterocyclic ring;

or a pharmaceutically acceptable salt thereof.

12. A compound as claimed in Claim 11, in which X^1 represents NH.

13. A compound as claimed in Claim 11 or Claim 12, in which L represents a bond or a group of formula C_mH_{2m}-$(X_3)_q$-C_nH_{2n} in which X^3 is O, S, SO, SO_2, NH, CHF, CF_2, CHOH, CH(O(1-4C)alkyl) or CO, q is 0 or 1, and each of m and n is 0 or an integer of from 1 to 4, provided that when q is 1 and X^3 is O, S, SO, SO_2 or NH, m is at least 2.

14. A compound as claimed in Claim 13, in which L represents a bond, $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, $-CH(CH_3)CH_2-$, or $-(CH_2)_2SCH_2-$.

15. A compound as claimed in Claim 13, in which L represents a bond or $-(CH_2)_2-$.

16. A compound as claimed in any one of Claims 11 to 15, in which R^1 represents an unsubstituted or substituted carbocyclic group in which the carbocyclic group is selected from an aromatic group, a non-aromatic group and a non-aromatic group fused with an aromatic group.

17. A compound as claimed in Claim 16, in which the carbocyclic group is selected from phenyl which is unsubstituted or substituted by one or two substituents selected independently from a halogen group, a (1-4C)alkyl group and a (1-4C)alkoxy group; (3-10C)cycloalkyl which is unsubstituted or substituted by from one to three methyl groups; 2,3-dihydro-1H-indenyl; and 1,2,3,4-tetrahydronaphthyl.

18. A compound as claimed in Claim 16, in which the carbocyclic group is selected from phenyl which is unsubstituted or substituted by one or two substituents selected independently from a halogen group, a (1-4C)alkyl group and a (1-4C)alkoxy group.

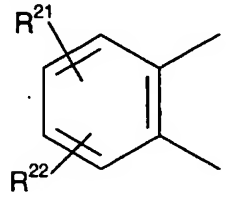
19. A compound as claimed in Claim 18 wherein the halogen group consists of F, Cl, and Br.

20. A compound as claimed in Claim 16, in which R^1 represents phenyl, 2-chlorophenyl, 3-bromophenyl, 2,6-

dichlorophenyl, 2-chloro-4-fluorophenyl, 2-methylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 4-phenylphenyl, cyclohexyl, bicyclo[2.2.1]hept-2-yl, (1R,2R,3R,5S)-2,6,6-trimethylbicyclo[3.1.1]hept-2-yl, adamantyl, 2,3-dihydro-1H-inden-1-yl, 2,3-dihydro-1H-inden-2-yl and 1,2,3,4-tetrahydronaphth-1-yl.

21. A compound as claimed in any one of Claims 11 to 20, in which R^2 represents a hydrogen atom, a halogen atom, a carboxy group, a cyano group, or a (1-8C)alkyl, halo(1-6C)alkyl, (1-6C)alkoxy, hydroxy(1-6C)alkoxy, (1-6C)alkylthio, (1-4C)alkylsulfonyl, (1-4C)alkylamino, halo(1-4C)alkylthio, hydroxy(1-4C)alkylthio, dihydroxy(1-4C)alkylthio, (1-4C)alkoxy(1-4C)alkylthio, (1-4C)alkanoyl(1-4C)alkylthio, (1-4C)alkoxycarbonyl(1-4C)alkylthio, carboxy(1-4C)alkylthio, (1-4C)alkylaminocarbonyl(1-4C)alkylthio, (1-4C)alkanoylamino(1-4C)alkylthio, (1-4C)alkylaminosulfonyl)(1-4C)alkylthio, di(1-4C)alkylaminophosphonyl)(1-4C)alkylthio, or phenyl(1-4C)alkylthio in which the phenyl group is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, (1-4C)alkyl and (1-4C)alkoxy.

22. A compound as claimed in any one of Claims 11 to 21 in which R^3 and R^4 together with the carbon atoms to which they are attached form a ring of formula:



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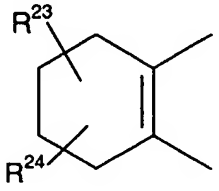

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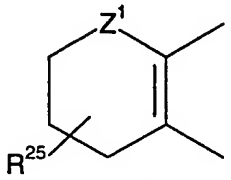

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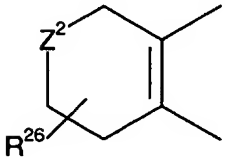

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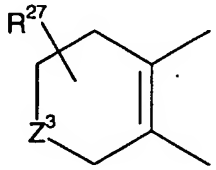

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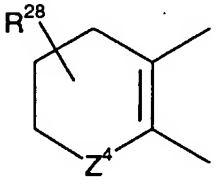

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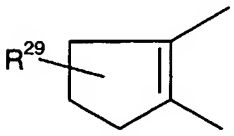

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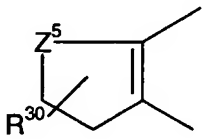

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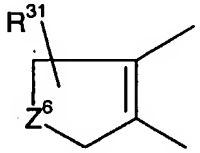

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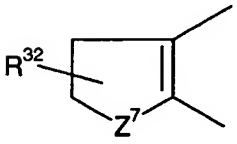

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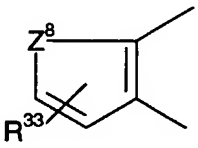

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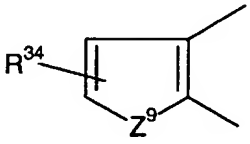

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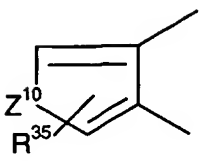

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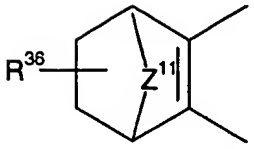

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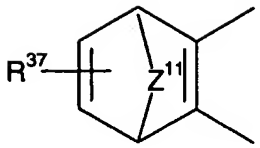

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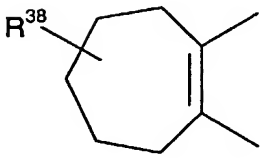


p

in which:

Z^1, Z^2, Z^3, Z^4, Z^5, Z^6, Z^7, Z^8, Z^9 and Z^{10} are each selected independently from O, NR^{41}, S, SO and SO_2;

Z^{11} represents O, S, CH_2 or CH_2CH_2;

R^{21} and R^{22} each independently represents a hydrogen atom, a halogen atom, a nitro group, a cyano group, a (1-4C)alkyl group, a halo(1-4C)alkyl group, or a group of formula $-X^4-R^{51}$ in which X^4 represents O, S, SO, SO_2, NR^{52}, CO, COO, OCO, CONH, NHCO, SO_2NH, or $NHSO_2$ and R^{51} represents a hydrogen atom, a (1-4C)alkyl group, a phenyl group or a phenyl(1-4C)alkyl group in which any phenyl group is unsubstituted or substituted by one or two substituents selected independently from a halogen atom, a (1-4C)alkyl group and a (1-4C)alkoxy group;

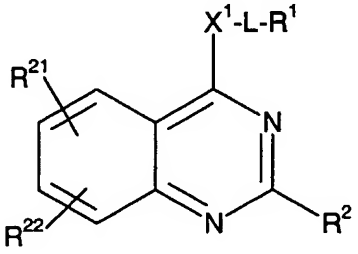
R^{23}, R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30}, R^{31}, R^{32}, R^{36}, R^{37} and R^{38} each independently represents a hydrogen atom, an oxo group, a halogen atom, a (1-4C)alkyl group, a halo(1-4C)alkyl group, an aryl(1-4C)alkyl group, a (1-4C)alkoxy(1-4C)alkyl group, a (1-4C)alkylthio group, a (1-4C)alkylsulfinyl group, a (1-4C)alkylsulfonyl group or a (1-4C)alkanoyl group;

R^{33}, R^{34} and R^{35} each independently represents a hydrogen atom, a halogen atom, a (1-4C)alkyl group or a (1-4C)alkoxy group;

R^{41} represents a (1-6C)alkyl group or a group of formula Y-R^a in which Y represents CO, COO or CONH and R^a represents (1-4C)alkyl, phenyl(1-4C)alkyl, phenyl(2-4C)alkenyl, (3-10C)cycloalkyl, or, when Y is CO, morpholino; and

R^{52} represents a hydrogen atom, a (1-4C)alkyl group or a phenyl(1-4C)alkyl group.

23. A compound as claimed in Claim 22, which is selected from compounds of formulae



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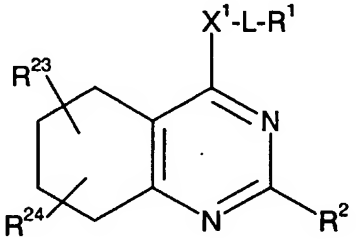

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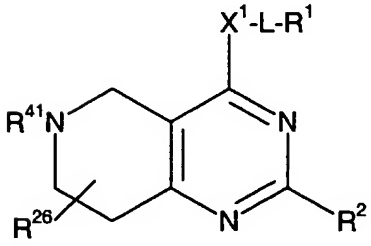
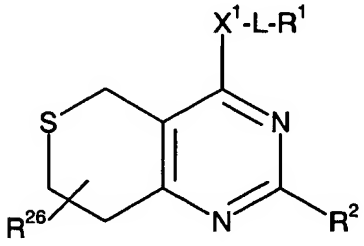


Id1



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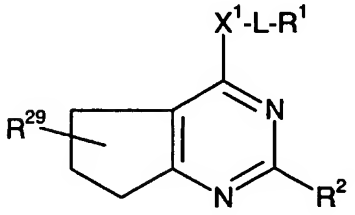

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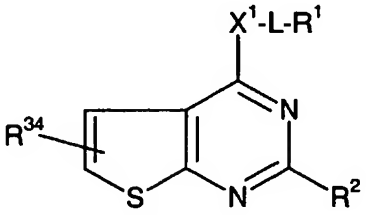

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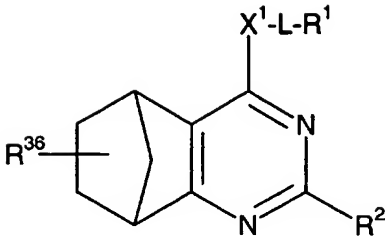

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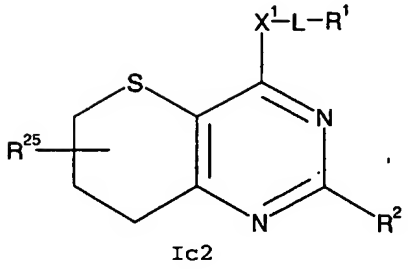

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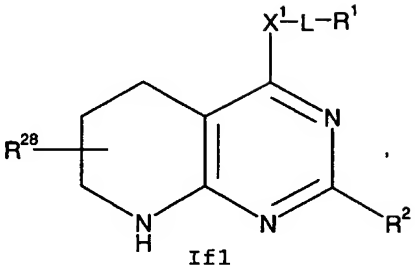

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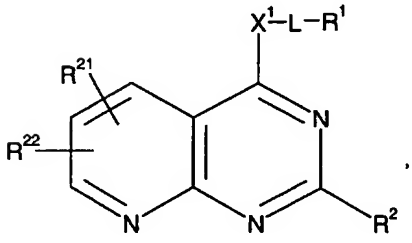

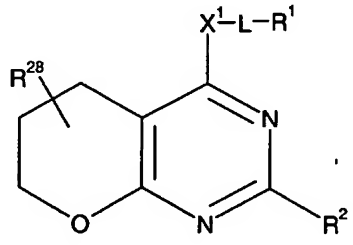

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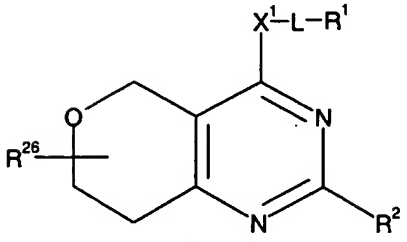
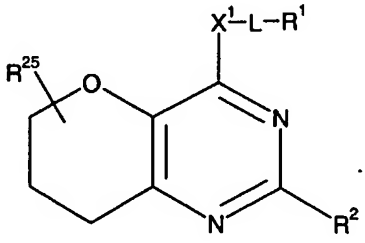


Id3

and

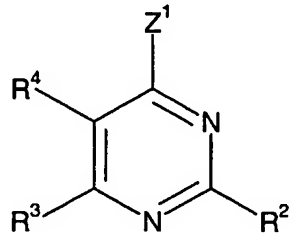


Ic2

24. A pharmaceutical formulation comprising a compound as claimed in any one of Claims 11 to 23, and a pharmaceutically acceptable carrier.

25. A process for the preparation of a compound as claimed in any one of Claims 11 to 23, which comprises

(a) reacting a compound of formula



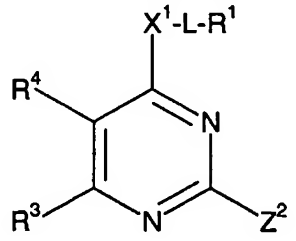
II

in which Z^1 represents a leaving atom or group, with a compound of formula

$$R^1\text{-}L\text{-}X^1H$$

III

(b) for a compound of formula I in which R^2 represents $X^2\text{-}R^5$, reacting a compound of formula



IV

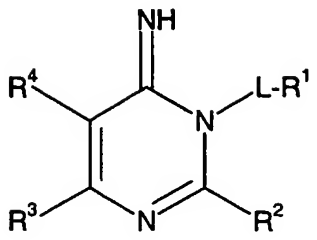
in which Z^2 represents a leaving atom or group with a compound of formula

$$HX^2\text{-}R^5$$

V

or a base salt thereof;

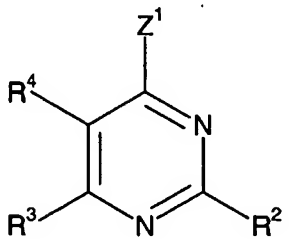
(c) for a compound of formula I in which X^1 represents NH, rearranging a compound of formula



VI

followed where desired by forming a pharmaceutically acceptable salt.

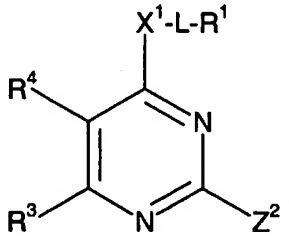
26. A compound of formula



II

in which Z^1 represents a leaving atom or group and R^2, R^3 and R^4 are as defined in Claim 11.

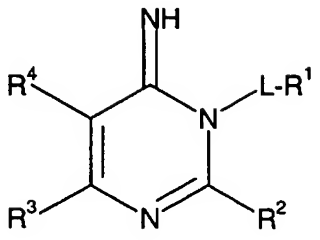
27. A compound of formula



IV

in which Z^2 represents a leaving atom or group and R^1, X^1, L, R^3 and R^4 are as defined in Claim 11.

28. A compound of formula



VI

in which R^1, R^2, L, R^3 and R^4 are as defined in Claim 11.

29. A method of treating pain, which comprises administering to a patient in need of treatment an effective amount of a compound as claimed in Claim 11.

30. A method of treating migraine, which comprises administering to a patient in need of treatment an effective amount of a compound as claimed in Claim 11.

31. A method of treating migraine, which comprises administering to a patient in need of treatment an effective amount of a selective mGluR1 antagonist.

32. The use of a selective mGluR1 antagonist for the manufacture of a medicament for the treatment of migraine.

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WO 01/32632 A3

(54) Title: PHARMACEUTICALLY ACTIVE 4-SUBSTITUTED PYRIMIDINE DERIVATIVES

(57) Abstract: The present invention relates to the use of certain 4-substituted pyrimidine derivatives as mGluR1 antagonists, to novel 4-substituted pyrimidine derivatives, to pharmaceutical formulations comprising 4-substituted pyrimidine derivatives, to a process for preparing 4-substituted pyrimidine derivatives and to intermediates useful in the preparation of 4-substituted pyrimidine derivatives.

INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/US 00/26261

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/94 C07D239/95 C07D471/04 C07D491/04 C07D495/04
C07D239/46 A61K31/517 A61P25/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	claims; examples 1-80	11,25,26
A	WO 97 49689 A (PHARMACIA & UPJOHN) 31 December 1997 (1997-12-31) page 1 -page 26	1
X	page 27 -page 44; claims 1,12,16	11,23, 25,26

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
22 May 2001	31/05/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

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INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/US 00/26261

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	claims; examples 1-100	11,12, 23,25,26

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